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Improved Antibody Response to Three Additional Hepatitis B Vaccine Doses Following Primary Vaccination Failure in Patients with Inflammatory Bowel Disease

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Abstract

Background—Studies have shown the efficacy of hepatitis B (HBV) vaccination in patients with inflammatory bowel disease (IBD) is impaired, but few data exist regarding the effectiveness of revaccination strategies following primary vaccination failure. Our aim was to analyze the association between administration of additional vaccine doses and hepatitis B surface antibody (HBsAb) seroconversion.

Methods—This is a retrospective cohort study. Inclusion criteria are as follows: age ≥ 18, diagnosis of Crohn's disease (CD) or ulcerative colitis (UC), inadequate HBsAb < 10 IU/L following initial HBV vaccination series, subsequent administration of 1–3 additional doses of HBV vaccine with follow-up serum HBsAb measurements. Patients were stratified into groups of ≤ 2 or 3 doses received. Primary outcome was achieving HBsAb > 10 IU/L. Outcomes were stratified by age ≥ or < 40 years. We performed logistic and linear multivariable regression analyses for categorical and continuous data.

Results—The study cohort consists of (n = 149) 54.4% women; 77.9% white; 72.6% with CD, with mean age: 46.2. Patients of all ages and age ≥ 40 years, who received 3 additional doses of vaccine, were more likely to achieve seroprotective HBsAb levels than patients who received 1 or 2 doses (OR 1.77, P = 0.01; OR 1.9, P = 0.03, respectively, after adjusting for age, sex, race, immunosuppressive medication exposure, time between vaccine/titer).

Conclusions—Following initial HBV vaccination failure, patients with IBD of all ages are more likely to develop seroprotective levels of HBsAb following 3 additional vaccine doses, rather than

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Author's contribution PKP were involved in the study conception and design, literature search and review, data collection, analysis and interpretation of data, drafting and revision of manuscript, final approval of version to be published, and agreement to be accountable. DN was involved in the analysis and interpretation of data, critical revision of manuscript, final approval of version to be published, and agreement to be accountable. MTL was involved in the analysis and interpretation of data, critical revision of manuscript, final approval of version to be published, and agreement to be accountable. FAF was involved in the study conception and design, literature search and review, analysis and interpretation of data, critical revision of manuscript, final approval of version to be published, and agreement to be accountable.

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1 or 2 alone. In patients who fail primary HBV vaccination, providers should consider a more aggressive revaccination strategy with an additional 3-dose series.

Keywords

Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Hepatitis B virus immunity; Hepatitis B virus vaccination failure; Booster; Revaccination

Introduction

Over the past decade, therapy for inflammatory bowel disease (IBD) has been redefined through the use of immunosuppressant and biologic therapies, including anti-tumor necrosis factor (anti-TNF) drugs, anti-integrins, IL 12/23 inhibitors, and JAK inhibitors [1]. These drugs are used more frequently and earlier in the disease course to treat IBD, and as a result of this immunosuppression, patients are at increased risk for infections, including reactivation of hepatitis B (HBV) [2]. It is known that the efficacy of vaccination against HBV in patients with IBD receiving immunosuppressive therapy is impaired [2–4]. Specifically, patients on immunosuppressive therapy have a reduced primary response to vaccination and accelerated loss of hepatitis B surface antibody (HBsAb) over time [2, 5]. When the HBsAb titers fall to < 10 international units/liter (IU/L), patients are at increased risk of HBV reactivation, which can range in severity from mild to fulminant [4, 6]. Currently, there are very few studies examining the effectiveness of various HBV revaccination strategies for patients with IBD.

The available studies on HBV revaccination focus on the utility of a single vaccination approach studied within a single cohort, and the resultant data are inconsistent and often difficult to interpret [2, 7–9]. In a cohort of children with IBD who were primary non-responders to HBV vaccination, a single-dose HBV "booster" vaccination had an efficacy of 75% [8]; however, studies in adults demonstrate a much lower efficacy, even if a complete 3-dose series is given [2, 7]. In contrast, Matsumoto et al. showed no improvement in immunogenicity among adult patients with IBD who received a second "booster" vaccination of trivalent influenza [9], suggesting adult patients with IBD may require more prolonged antigen exposure. In a cohort of pediatric patients with human immunodeficiency virus (HIV) infection, only 14% of initial HBV vaccine non-responders seroconverted after receiving an additional booster vaccination [10], whereas adults with HIV had improved seroconversion rates after a three-dose vaccine series [11]. Although it is well established that 25–50% of immunocompetent HBV vaccine non-responders will subsequently respond to an additional vaccine dose [12], the response rate of immunocompromised patients with IBD to the same "booster" remains unclear. Due to the lack of available data, professional societies, such as the American College of Gastroenterology (ACG), the Infectious Disease Society of America (IDSA), and the Advisory Committee on Immunization Practices (ACIP), offer very little guidance on revaccination strategies for immunocompromised patients with IBD, often relying upon expert opinion [12–14].

The aim of our study was to analyze the association between administration of additional HBV vaccine doses and HBsAb seroconversion in adult patients with IBD following initial

vaccination failure. It is our hypothesis that additional doses of vaccine may be associated with an improved response across all age groups.

Materials and Methods

Study Sample

We conducted a retrospective cohort study of patients with inflammatory bowel disease who had failed to develop protective antibody titers following primary vaccination against HBV. Patients with IBD followed in the Section of Gastroenterology at Boston Medical Center between January 2000 and December 2014 were included in our IRB-approved study.

Patient charts were identified and relevant information retrospectively extracted using our institution's electronic database. Initial search criteria included ICD-9 (International Classification of Disease, Ninth Revision) codes 555.xx and 556.xx, as well as either: (1) hepatitis B surface antibody (HBsAb) > 0, or (2) documented vaccination against HBV (using Current Procedural Technology (CPT) diagnostic coding, published by the American Medical Association).

Inclusion and Exclusion Criteria

Given our immunosuppressed patient population, our study defined inadequate HBV seroprotection as HBsAb < 10 IU/L.

Inclusion criteria for our study included (1) diagnosis of Crohn's disease or ulcerative colitis (per ICD-9 coding) and (2) inadequate HBV seroprotection following prior HBV vaccination, referred to as primary vaccination failure. Documentation in our EMR of a prior HBV vaccination and/or ≥ 1 HBsAb titers > 0 IU/L and < 10 IU/L) constituted evidence of prior HBV vaccination. Additional inclusion criteria were (3) subsequent administration of one or more additional HBV vaccine doses (2 doses needed to have been administered within 6 months, or 3 doses given within 12 months); and (4) electronic record of titer level measurement following additional HBV vaccine doses. Following primary vaccination failure, the number of additional revaccination attempts was left to the discretion of the treating clinician.

Exclusion criteria were: (1) positive hepatitis B surface antigen (HBsAg); (2) positive hepatitis B core antibody (HBcAb); (3) age below 18 years; (4) HIV; (5) chronic kidney disease requiring hemodialysis; (6) other autoimmune disease requiring immunosuppression; and (7) electronic record of HBsAb titer levels measured in between subsequent revaccination attempts. Although this study is retrospective, this last criterion was an attempt to limit selection bias by the treating clinician (i.e., selecting which patients would require further revaccination attempts).

Exposures

Our chart review focused on recording HBsAb titer levels drawn following both primary vaccination series and revaccination attempts. Patients were categorized according to the number of HBV revaccination doses received, following initial HBV vaccination failure (≤ 2 vs 3 doses). Of note, in our study, double-dose revaccinations given on the same day were

categorized as 2 separate doses/revaccination attempts. Study arms included: (1) 1 or 2 doses (administered sequentially within 6 months) and (2) 3 doses (administered within 12 months). Given the known association between immunosuppressive IBD medications and impaired response to HBV vaccination, several types of IBD medications prescribed to patients in the 6 months prior to titer level measurement were also recorded—including anti-TNFs, immunomodulators (thiopurines and methotrexate), dual therapy, and corticosteroids [2–4].

In addition, interval time between vaccination and titer level measurement was collected to help adjust for serum titers that are expected to wane with time. Demographic data were collected, including patient age (at diagnosis and at time of titer measurement), sex, race, and body mass index (BMI).

Primary Outcome

Our primary outcome was the presence of seroprotective HBsAb titer following revaccination of IBD patients against HBV. Revaccination attempts were administered sequentially without titer levels drawn in between, and titer levels of interest were measured following completion of revaccination. Seroprotection was assessed as a categorical variable, using a single HBsAb serum titer cutoff: > 10 IU/L (standard definition of adequate seroprotection) [3]. As a secondary outcome, post-vaccination serum titer levels were recorded and assessed as a continuous variable. Of note, our primary and secondary outcomes explored single titer levels and not titer kinetics over time or in response to vaccination.

Statistical Analysis

To describe the characteristics of the analysis sample, we used means with standard deviations (SD) for continuous data and percentages for categorical data. Categorical data were compared using the Chi-square test. We performed multivariable logistic regression models to assess the association between number of HBV revaccination doses (≤ 2 vs 3 doses) and HBV seroprotection. In the *"base model,"* we adjusted for demographic variables including age, sex, and race. In the *"multivariable model,"* we adjusted for age, sex, race, BMI, immunosuppressant drug exposure (specifically, anti-TNF, immunomodulator, dual therapy, and corticosteroids) and interval time between revaccination and titer level measurement. We also performed multivariable linear regression models to measure the association between number of HBV booster doses and HBsAb titer level (measured continuously) accounting for the same variables described above. Of note, we analyzed the same number of patients ($n = 149$) in each of our multivariable analyses. Given known strong associations in the literature between patient age and inadequate response to HBV vaccination, a secondary analysis was performed, stratifying data by patient age at a cutoff of 40 years [12, 15]. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) software. A 2-tailed P value of < 0.05 was considered significant.

Results

Our database search yielded an initial study sample of 770 patients. Following extensive chart review and per inclusion/exclusion criteria, our final analysis included 149 patients.

Characteristics of the study cohort (n = 149) are shown in Table 1. The mean age was 46.2 ± 15.1 years. 63.1% (n = 94/149) of the sample was older than age 40 years. Women comprised 54.4% (n = 81/149) of our study sample, and 77.9% of patients were white. 72.6% of patients had Crohn's disease, and 27.4% had ulcerative colitis. Overall, 58.4% (n = 87/149) of patients received 1 or 2 sequential HBV revaccination doses within a 6-month time period, and 41.6% (n = 62/149) of patients received 3 sequential revaccination doses during a 12-month time period.

During the 6 months prior to serum titer measurement, 78.5% of patients were exposed to some form of immunosuppressive IBD therapy. Specifically, 57.0% were exposed to immunomodulator therapy alone, 46.3% to anti-TNF therapy alone, 26.2% to dual therapy (anti-TNF + IMM), and 17.4% to corticosteroid therapy. Of note, when comparing our two study arms, a higher percentage of patients were exposed to each type of immunosuppressive IBD medication within our ≤ 2 dose arm compared with our 3-dose arm.

Table 2 summarizes our descriptive data, regarding HBsAb level, stratified by number of HBV revaccination attempts and patient age at time of titer level measurement. Overall, 49.7% of all patients seroconverted to HBsAb > 10 IU/L with mean serum HBsAb titer of 162.5 IU/L, after receiving any number of additional HBV vaccination doses. Among patients who received 1 vaccination dose, 41.3% developed HBsAb > 10 IU/L, and among those who received 2 vaccination doses, 40.0% seroconverted. Among patients who received 1 or 2 vaccination doses, 40.2% subsequently seroconverted, with a mean serum titer of 93.3 IU/L. This is compared with patients who received 3 vaccination doses, of which 62.9% seroconverted (P < 0.01), with a mean serum titer of 259.6 IU/L (P < 0.001).

Primary Analysis

In our multivariable logistic regression analysis, we observed a positive and statistically significant association between the number of revaccination doses received by a patient and subsequent HBsAb seroconversion (Table 3). In our *"base model,"* patients receiving 3 doses of HBV vaccination demonstrated nearly twofold increased odds of achieving immunity compared to those receiving only 1 or 2 doses (OR 1.95; 95% CI 1.27–2.99; P = 0.002). After accounting for additional covariates in our *"multivariable model,"* our results were slightly attenuated but remained statistically significant for patients of all ages (OR 1.77; 95% CI 1.12–2.80; P = 0.01).

When considering HBsAb as a continuous variable in our multivariable linear regression analysis, we also observed a positive and statistically significant association between the number of revaccination doses and post-vaccination serum HBsAb titer level (Table 4). In our *"base model"* analysis, the mean post-vaccination serum titer level increased by 107.29 IU/L in those who received 3 doses of vaccination, when compared to 1 or 2 doses (β

107.29; SE 25.51; $P < 0.0001$). Our *"multivariable model"* analysis of the same yielded similar statistically significant findings (β 116.29; SE 27.56; $P < 0.0001$).

Secondary Analysis

We performed a secondary analysis, stratifying by patient age (Tables 3, 4). We used an age cutoff of 40 years owing to the results of prior vaccination research which utilized the same [12, 15], and also in part due to the median age of our study cohort.

In the re-analysis of our descriptive data, we found a significantly greater proportion of patients of age ≥ 40 years seroconverted following 3 vaccination doses, compared with 1 or 2 (53.7% vs. 32.1%, $P < 0.04$). The data also demonstrated significantly higher mean follow-up serum titers for patients of age ≥ 40 years following 3 doses, compared with 1 or 2 (152.7 IU/L vs. 42.8 IU/L, $P < 0.01$). Similarly, for patients of age < 40 years, a significantly greater proportion of patients seroconverted following 3 vaccination doses (81.0% vs. 52.9%, $P < 0.04$), also demonstrating significantly higher mean follow-up serum titers (468.3 IU/L vs. 172 IU/L, $P < 0.01$).

Regarding our multivariable logistic regression analysis of our categorical data, our findings were similar after being stratified by patient age. We found a positive and statistically significant association between the number of revaccination doses received by a patient and subsequent HBsAb seroconversion. Under our *"base model"* multivariable analysis, we found similar results for both patients of age ≥ 40 years (OR 1.96; 95% CI 1.13–3.41; $P = 0.02$) and patients of age < 40 years (OR 2.18; 95% CI 1.05–4.52; $P = 0.04$). Under our *"multivariable model,"* we found a positive and statistically significant association only for patients of age ≥ 40 years (OR 1.90; 95% CI 1.05–3.43; $P = 0.03$).

Regarding our multivariable linear regression analysis of the continuous data, our findings were also similar after being stratified by patient age. Under our *"base model"* analysis, both age groups showed significant increases in post-vaccination serum titers: patients of age ≥ 40 years (β 81.77; SE 24.67, $P = 0.001$), and patients of age < 40 years (β 145.32; SE 54.04; $P = 0.01$). Our *"multivariable model"* analysis, again, showed statistically significant post-vaccination increases in serum HBsAb titer levels: patients of age ≥ 40 years (β 89.23; SE 26.52; $P = 0.001$) and patients of age < 40 years (β 181.1; SE 64.73; $P = 0.007$).

Discussion

In this retrospective study of immunocompromised patients with inflammatory bowel disease who had previously failed primary vaccination against HBV, we demonstrated an improved immune response in patients who received three additional revaccination doses, when compared with only one or two doses. More specifically, following multivariable regression analysis patients showed significantly higher rates of subsequent seroconversion to HBsAb > 10 IU/L. While 62.9% of patients responded to a 3-dose revaccination schedule, only 40.2% of our patients achieved seroprotective antibody levels after receiving only 1 or 2 doses. In addition, patients showed higher mean post-vaccination titer levels following a 3-dose revaccination schedule. Our findings are novel, in that we examined two HBV revaccination strategies within the same immunocompromised patient cohort, with one

proving superior across all measured outcomes. In our secondary analysis, we demonstrated similar findings among the same patient cohort but when stratified by patient age greater or less than 40 years. Patients aged ≥ 40 years responded significantly to the 3-dose revaccination strategy, though less well than those < 40 years of age, in terms of seroconversion rate and mean follow-up titer level.

Over the past decade, a number of studies have demonstrated the low rate of seroconversion following primary vaccination against HBV among patients with IBD [2–5]. However, there are very few studies examining the effectiveness of various revaccination strategies for patients with IBD. In 2015, Cossio-Gil et al. [7] showed that 52.8% of patients with IBD who initially failed HBV vaccination, went on to achieve protective antibody levels following an additional three scheduled doses, with patient age being the only independent predictor of non-response. Separately, Gisbert et al. [2] studied an alternative approach: an accelerated, double-dose revaccination protocol, which resulted in successful seroconversion (HBsAb > 10 IU/l) in 50% of initial non-responders. Overall, our data are consistent with the findings of the aforementioned studies, in which we showed 62.9% of patients, who initially failed HBV vaccination, to have subsequently developed protective titers following revaccination with a full 3-dose series.

Among immunocompetent patients who do not respond to an initial 3-dose HBV vaccination schedule, meta-analyses have reported that between 25 and 50% will respond to an additional booster vaccine dose, while between 44 and 100% will respond to a repeat 3-dose vaccine series [12]. While nowhere near 100%, the percentage of immunocompromised patients with IBD within our study who seroconverted following 3 sequential revaccination doses (62.9%) is well within the expected range of seroconversion for immunocompetent patients, as reported by the ACIP [12]. This revaccination success rate is remarkably high—especially as we are comparing immunocompetent with immunocompromised patients, and given the multitude of data published regarding the poor immunogenicity of patients with IBD on immunosuppressive therapy [2, 4, 7, 14, 16, 17].

Described differently, our multivariable analysis demonstrated that for patients of all ages, rather than 1 or 2 doses, following a 3-dose revaccination sequence: (i) the likelihood of seroconversion rose by a factor of 1.8, and (ii) post-vaccination HBsAb titer levels rose by a mean of 116 IU/L. In 2000, similar results were described by Rey et al. [11] in HIV-positive patients on stable anti-retroviral therapy, where only 55% of patients seroconverted following an initial 3-dose HBV vaccination series, yet 78% of those non-responders proceeded to seroconvert following an additional three doses. Similar to our study findings, in a population of immunocompromised patients at increased risk for HBV infection, increasing the number of vaccination attempts or duration of antigenic exposure was associated with an improvement in HBsAb response rates.

Patient age has previously been identified as a strong independent risk factor for impaired response to HBV vaccination [7, 12, 18]. In our secondary analysis, patients were stratified according to age greater than or less than 40 years, a threshold shown previously to be associated with a declining rate of seroconversion [12]. As might be expected, our data show younger patients of age < 40 years to have achieved significantly improved seroconversion

rates and post-vaccination titer levels following a 3-dose strategy, as opposed to a 1- or 2-dose strategy. Somewhat surprising, however, is that our data show older patients of age ≥ 40 years to have performed nearly (though not quite) as well as the younger cohort, again, in terms of seroconversion rate and post-vaccination titer levels. Important findings are as follows: (1) These data are consistent with the well-accepted negative association between patient age and vaccine responsiveness [2, 3, 7, 12], and (2) despite this, in our study a 3-dose revaccination strategy remained effective among, not only younger, but also older patients.

Per existing guidelines, all patients with IBD should be screened for active HBV infection and appropriately vaccinated against HBV with a 3-dose vaccination schedule, as early as possible and prior to initiation of immunomodulator or biologic therapies. Based upon our data, in clinical practice we would recommend that patients with IBD have serum HBsAb checked following initial vaccination, and if serum antibody titers are < 10 IU/L, repeat a full 3-dose vaccination schedule at that time.

Our study has several limitations. Most notably, it was not a randomized study and as a result there were differences in our patient study arms. While we accounted for known or suspected confounders, we were unable to account for unmeasured confounders, likely resulting in residual confounding. The associations we have described will aid in the design of future prospective and controlled studies. Another limitation is our inability to reliably distinguish between primary HBV vaccination non-responders and initial responders with waning antibody titers but ability to mount an anamnestic response once re-challenged with a booster vaccination. Also, an incomplete EMR database may have provided us with partial vaccination and medication histories, as we did not have access to vaccination/titer data performed outside of our own medical system. Additional booster vaccinations and/or IBD therapies administered elsewhere were unaccounted for and could have affected the results of our primary outcomes. Prior complete HBV vaccination series were often inferred based upon inadequate HBsAb levels and negative HBsAG and HBcAb status, and in these cases, it is unknown how patients responded to initial vaccination or the exact time interval between initial vaccination and revaccination. A number of revaccination doses received by patients were administered within a set period of time but were not administered according to a strict vaccination schedule. This was unable to be adjusted for and could have contributed to differences observed in our primary outcomes. Given the available data, our main outcome explored single titer levels at a given point in time and was not dynamic or related to seroconversion/titer kinetics over time.

Our study is retrospective and observational in design, limiting the conclusions that can be drawn from the data. Additional research is certainly warranted. For example, studies are needed to better understand the strength of the anamnestic response in immunocompromised individuals despite waning HBsAb titer levels, perhaps in relation to the strength of a patient's immunologic response to initial HBV vaccination. Also, as the goal of our current study is to prevent new infection with HBV in immunocompromised patients, further population-based studies are needed in the future to reassess the incidence of such, following incorporation of more aggressive HBV serologic screening and revaccination into clinical practice.

In summary, our findings suggest that following primary HBV vaccination failure, adults of all ages with IBD are more likely to develop seroprotective levels of HBsAb following three additional vaccine doses, rather than 1 or 2 alone. Our data support the conclusion that a 3-dose revaccination strategy rather than a 1- or 2-dose strategy leads to higher mean serum titer levels and, as a result, a greater likelihood of reaching a seroprotective level. In addition, our analysis suggests the efficacy of the 3-dose strategy is generalizable to patients older than 40 years, an age group that is often more difficult to properly vaccinate. Overall, in patients with IBD, immune response to vaccination against HBV involves a complex interplay between the strength of the host immune status, vaccination timing, effects of immunosuppressant therapy, patient age, and more [2, 3, 5, 15, 16]. As these patients are oftentimes challenging to effectively vaccinate against hepatitis B virus, a more aggressive approach to revaccination may be warranted.

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Table 1

Baseline characteristics

	Overall (*n* = 149)	**1 or 2 HBV revaccination doses administered (*n* = 87)**	**3 HBV revaccination doses administered (*n* = 62)**
Mean age, at titer measurement	46.2 (15.1)	44.9 (14.9)	48.1 (15.2)
Age ≥ 40 years (%)	63.1	60.9	66.1
Women (%)	54.4	54.0	54.8
Race/ethnicity			
White (%)	77.9	75.9	80.6
Mean BMI (kg/m^2)	28.0 (5.9)	27.5 (6.3)	28.7 (5.1)
Type of colitis			
Crohn's disease (%)	72.6	71.3	76.3
Mean/median interval time (days)[+]	678.0/277	260.6/203.5	1061.2/471
IBD medication exposures[±]			
Any therapy (%)[§]	78.5	83.9	71.0
Immunomodulator (%)[¶]	57.0	60.9	51.6
Anti-TNF	46.3	51.7	38.7
Dual therapy[++]	26.2	28.7	22.6
Corticosteroids[±±]	17.4	19.5	14.5

[+]Interval time between last vaccination received and titer measurement

[±]Drug exposures within 6 months of titer level measurements

[§]Including immunomodulator, anti-TNF, and corticosteroid therapy

[¶]Including azathioprine, 6-mercaptopurine, and methotrexate therapy

[++]Immunomodulator therapy and anti-TNF therapy

[±±]Including prednisone (po), budesonide (po/pr), and hydrocortisone therapy (po/pr)

HBV hepatitis B virus, *BMI* body mass index, *IBD* inflammatory bowel disease, *anti-TNF* anti-tumor necrosis factor

Table 2

Descriptive data

	Overall (*n* = 149)	1 or 2 HBV revaccination doses administered (*n* = 87)	3 HBV revaccination doses administered (*n* = 62)	*p* value
Seroconversion to HBsAb > 10 IU/L				
All ages, %	49.7	40.2	62.9	< 0.01
Age < 40 years, %[+]	63.6	52.9	81	< 0.04
Age ≥ 40 years, %[+]	41.5	32.1	53.7	< 0.04
Mean follow-up HBsAb titer				
All ages, IU/L (SD)	162.5 (299.8)	93.3 (200.0)	259.6 (379.0)	< 0.001
Age < 40 years, IU/L (SD)[+]	285.1 (391.5)	172.0 (283.5)	468.3 (465.8)	< 0.01
Age ≥ 40 years, IU/L (SD)[+]	91.7 (197.7)	42.8 (87.1)	152.7 (269.1)	< 0.01

[+]Performed as part of secondary analysis

HBV hepatitis B virus, *HBsAb* hepatitis B surface antibody, *IU/L* international units/liter, *SD* standard deviation

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Table 3

Association between number of additional HBV vaccine doses and HBV immunity

	Base model[±]		Multivariable model[§]	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
All ages	1.95 (1.27, 2.99)	< 0.01	1.77 (1.12, 2.80)	0.01
Age < 40 years[+]	2.18 (1.05, 4.52)	< 0.05	1.90 (0.83, 4.39)	0.13
Age > 40 years[+]	1.96 (1.13, 3.41)	< 0.05	1.90 (1.05, 3.43)	< 0.05

[+]Performed as part of secondary analysis

[±]Base model adjusted for patient age, sex, and race

[§]Multivariable model adjusted for patient age, sex, race, BMI, immunosuppressive drug exposure, and interval time between vaccination and titer level measurement

HBV hepatitis B virus, *OR* odds ratio, *CI* confidence interval

Table 4

Association between number of additional HBV vaccine doses and follow-up HBsAb titer level

	Base model[±]		Multivariable model[§]	
	β (SE)	***P* value**	**β (SE)**	***P* value**
All ages	107.29 (25.51)	< 0.001	116.29 (27.56)	< 0.001
Age < 40 years[+]	145.32 (54.04)	0.01	181.1 (64.73)	< 0.01
Age ≥ 40 years[+]	81.77 (24.67)	0.001	89.23 (26.52)	0.001

[+] Performed as part of secondary analysis

[±] Base model adjusted for patient age, sex, and race

[§] Multivariable model adjusted for patient age, sex, race, BMI, immunosuppressive drug exposure, and interval time between vaccination and titer level measurement

HBV hepatitis B virus, β beta-coefficient, *SE* standard error