



Risk of Hepatitis B Virus (HBV) Reactivation in Patients with Immune-Mediated Inflammatory Diseases Receiving Biologics: Focus on the Timing of Biologics after Anti-HBV Treatment

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Background/Aims: Anti-hepatitis B virus (HBV) therapy is required for patients with HBV infection receiving biologics because of the high risk of HBV reactivation. However, it is unclear when to start biologics after anti-HBV treatment. We investigated the risk of HBV reactivation according to the timing of biologics initiation after anti-HBV treatment in immune-mediated inflammatory disease (IMID) patients with HBV infection.

Methods: We retrospectively evaluated the incidence of HBV reactivation in IMID patients who received biologics between July 2005 and April 2020. The patients were divided into two groups (within 1-week and after 1-week) according to the timing of biologics initiation after anti-HBV treatment. The cumulative probabilities and factors associated with HBV reactivation were evaluated.

Results: A total of 60 hepatitis B surface antigen-positive patients with IMID received biologics (within 1-week group, n=23 [38%]; after 1-week group, n=37 [62%]). During a median follow-up of 34 months (interquartile range, 20 to 74 months), three patients (5%) developed HBV reactivation. In univariate analysis, the timing of biologics after anti-HBV treatment was not significantly associated with the risk of HBV reactivation (hazard ratio, 0.657; 95% confidence interval, 0.059 to 7.327; p=0.733). The cumulative probabilities of HBV reactivation did not significantly differ according to the timing of biologics (p=0.731).

Conclusions: The risk of HBV reactivation was not significantly associated with the timing of biologics administration after anti-HBV treatment. Thus, biologics may be initiated early in patients with IMID undergoing treatment for HBV. (*Gut Liver* 2022;16:567-574)

Key Words: Hepatitis B virus; Biologics; Immune-mediated inflammatory disease; Tumor necrosis factor inhibitor

INTRODUCTION

Biologics such as anti-tumor necrosis factor (TNF)- α agents are widely used to treat patients with immune-mediated inflammatory diseases (IMIDs) including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.¹⁻³ The introduction of biologics led to significant improvements in the treatment of IMID, but has been shown to accompany increased risk of infection including the reactivation of latent tuberculosis infection.^{4,5}

Hepatitis B virus (HBV), a hepatotropic DNA virus, can

infect hepatocytes and reside inside the nucleus as a form of covalently closed circular DNA, which is responsible for the chronic and persistent nature of HBV infection.⁶ HBV infection is one of the major causes of chronic liver disease, which is a global public problem with a higher prevalence in Asian countries.⁷ In addition, with the recent widespread use of biologics, there has been attention to the reactivation of HBV in patients with IMID. Recent guidelines recommend that patients with HBV infection—particularly those positive for hepatitis B surface antigen (HBsAg)—should receive anti-HBV treatment when us-



ing biologics.⁸⁻¹² However, it is not well established when anti-HBV treatment should be started before biologics use, although it is often suggested to administer anti-HBV agents at least 1 week before initiating immunosuppressive therapy.^{10,13}

No studies to date have directly compared the risk of HBV reactivation according to the timing of biologics administration after the initiation of anti-HBV treatment. We hypothesized that the risk of HBV reactivation would not be high even if biologics were initiated after a relatively short HBV treatment period of less than 1 week. Therefore, we investigated whether biologics can be initiated early with anti-HBV agents in patients with IMIDs by comparing the incidence of HBV reactivation between patients who received biologics within 1 week and those who received it at least 1 week after anti-HBV treatment.

MATERIALS AND METHODS

1. Patients

In this retrospective cohort study, we reviewed the data of HBsAg-positive patients with IMIDs who were started on biologics between July 2005 and April 2020 at Asan Medical Center, a tertiary referral hospital in Seoul, Korea. The definition of IMID included the following diseases: rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, and other rheumatic diseases such as systemic lupus erythematosus and adult-onset Still's disease. The following data were collected from the electronic medical records: demographic information (sex, age, body mass index, comorbid diseases [hypertension, diabetes mellitus]), drug exposure (corticosteroids, azathioprine, disease-modifying anti-rheumatic drugs including methotrexate, sulfasalazine, and hydroxychloroquine) and baseline laboratory data (HBV DNA titers, HBV antibody profile, and aspartate aminotransferase, alanine aminotransferase, total bilirubin). Data on the type of anti-HBV agents were also collected.

Patients were classified into two groups (within 1-week group vs after 1-week group) according to the timing of biologics administration after initiating anti-HBV therapy. HBV reactivation is defined as increases in the HBV DNA titers by more than 100-fold compared with the lowest level of HBV DNA titers or measurement of more than 1,000 IU/mL in a patient with a previously undetectable level of HBV DNA.¹⁰

Patients were excluded if they had any of the following: positive serology for hepatitis C virus, human immunodeficiency virus, or a history of acute hepatitis A infection.

This study was approved by the Institutional Review

Board of Asan Medical Center (IRB number: 2020-1738). The requirement for informed consent was waived due to the retrospective design of the study.

2. Statistical analysis

The chi-square and the Fisher exact tests were used to compare categorical data. Continuous values are expressed as mean (standard deviations or as median [interquartile range]) and were compared using the Student t-test for parametric data and the Mann-Whitney U test for nonparametric data. To identify the risk factors for HBV reactivation, the univariate Cox regression analyses were performed and the results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). The cumulative probabilities of HBV reactivation were calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at $p < 0.05$. All statistical analyses were performed in IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics of patients with IMID and HBV infection receiving biologics

A total of 60 IMID patients with HBsAg-positive were included in this study. The baseline clinical and laboratory data of the patients are summarized in Table 1. The mean age was 47.7 ± 10.4 years and 32 patients (53.3%) were female. The most common type of IMID was rheumatoid arthritis (38.3%), followed by Crohn's disease (33.3%), ulcerative colitis (13.3%), and ankylosing spondylitis (11.7%). Of the biologics, anti-TNF- α agents (17 etanercept, 18 infliximab, 18 adalimumab, and two golimumab) were administered to 55 patients (91.7%).

Of the total patients, 23 patients (38.3%) were started on biologics within 1 week of anti-HBV treatment initiation and were thus included in the "within 1-week group," and the remaining 37 patients (61.7%) were included in the "after 1-week group." The majority of patients (78.3%) in the within 1-week group received biologics and anti-HBV agents at the same time. The mean age at the treatment of biologics was significantly younger in the within 1-week group than in the after 1-week group (43.8 years vs 50.1 years, $p = 0.022$). The distribution of the types of IMID was significantly different between the two groups ($p = 0.030$), whereas there were no significant differences in the biologics and medications including corticosteroids and disease-modifying anti-rheumatic drugs. There were no significant differences in the HBV serology and liver function test results between the two groups, except the baseline median

Table 1. Clinical Characteristics of the Study Patients

Characteristics	Total (n=60)	Within 1-week group (n=23)	After 1-week group (n=37)	p-value
Age, yr	47.7±10.4	43.8±10.0	50.1±10.0	0.022
Female sex	32 (53.3)	15 (65.2)	17 (45.9)	0.146
BMI, kg/m ²	22.9±3.8	22.8±4.6	23.0±3.3	0.785
IMIDs				0.030
Rheumatoid arthritis	23 (38.3)	9 (39.1)	14 (37.8)	
Ankylosing spondylitis	7 (11.7)	5 (21.7)	2 (5.4)	
Crohn's disease	20 (33.3)	9 (39.1)	11 (29.7)	
Ulcerative colitis	8 (13.3)	0	8 (21.6)	
Others	2 (3.3)	0	2 (5.4)	
Biologics				0.593
Anti-TNF- α agents	55 (91.7)	22 (95.7)	33 (89.2)	
Etanercept	17 (28.3)	7 (30.4)	10 (27.0)	
Infliximab	18 (30.0)	4 (17.4)	14 (37.8)	
Adalimumab	18 (30.0)	10 (43.5)	8 (21.6)	
Golimumab	2 (3.3)	1 (4.3)	1 (2.7)	
Tocilizumab	2 (3.3)	0	2 (5.4)	
Rituximab	1 (1.7)	0	1 (2.7)	
Ustekinumab	1 (1.7)	0	1 (2.7)	
Tofacitinib	1 (1.7)	1 (4.3)	0	
Corticosteroids	31 (51.7)	9 (39.1)	22 (59.5)	0.126
Prednisolone, mg/day	2.5 (0–10)	0 (0–10)	5.0 (0–20)	0.053
Prednisolone \geq 10 mg/day	21 (35.0)	6 (26.1)	15 (40.5)	0.254
Anti-inflammatory drugs	29 (48.3)	11 (47.8)	18 (48.6)	0.951
DMARDs	21 (35.0)	8 (34.8)	13 (35.1)	0.978
Azathioprine	8 (13.3)	3 (13.0)	5 (13.5)	1.000
Comorbidities				
Hypertension	5 (8.3)	0	5 (13.5)	0.146
Diabetes mellitus	3 (5.0)	2 (8.7)	1 (2.7)	0.552
Liver-related characteristics				
Cirrhosis	8 (13.3)	1 (4.3)	7 (18.9)*	0.138
Decompensated cirrhosis	2 (28.6)	0	2 (33.3)	1.000
Laboratory findings (at anti-HBV agent initiation)				
HBV DNA, IU/mL	5.5×10 ³ (2.6×10 ² –7.6×10 ⁷)	5.4×10 ² (2.0×10 ² –5.6×10 ⁵)	5.7×10 ⁶ (4.0×10 ² –2.0×10 ⁸)	0.071
ALT, IU/L	28 (12–101)	18 (12–32)	87 (11–142)	0.048
AST, IU/L	27 (19–86)	23 (18–28)	58 (19–112)	0.008
Total bilirubin, mg/dL	0.6 (0.4–0.9)	0.6 (0.4–0.7)	0.7 (0.4–0.9)	0.108
Baseline laboratory findings (at biologics initiation)				
HBeAg positive	15 (25.0)	7 (30.4)	8 (21.6)	0.443
HBV DNA, IU/mL	2.1×10 ² (0 [†] –4.6×10 ³)	5.4×10 ² (2.0×10 ² –5.6×10 ⁵)	3.7×10 ¹ (0 [†] –4.3×10 ²)	0.001
HBV DNA (>2,000 IU/mL)	15 (25.0)	9 (39.1)	6 (16.2)	0.046
ALT, IU/L	22 (18–28)	18 (13–29)	14 (10–24)	0.088
AST, IU/L	14.5 (11–24)	25.0 (18–25)	21.0 (18–30)	0.428
Total bilirubin, mg/dL	0.6±0.2	0.6±0.2	0.5±0.2	0.527

Data are presented as the mean±SD, number (%), or median (interquartile range).

BMI, body mass index; IMID, immune-mediated inflammatory disease; TNF, tumor necrosis factor; DMARDs, disease-modifying anti-rheumatic drugs; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen.

*Including hepatocellular carcinoma (n=1); [†]Undetectable serum HBV DNA.

HBV DNA titers were higher in the within 1-week group (5.4×10^2 IU/mL vs 3.7×10^1 IU/mL, $p=0.001$).

2. Development of HBV reactivation

Table 2 shows the occurrence of HBV reactivation during biologic treatment with anti-HBV therapy. Follow-up duration was significantly longer in the within 1-week

group than in the after 1-week group (50.0 months [interquartile range, 31 to 86] vs 25.0 months [interquartile range, 17 to 70], $p=0.026$). The most common antiviral agents prescribed for HBV were entecavir (41.7%) and tenofovir (41.7%), followed by lamivudine (15.0%) and telbivudine (1.7%). The types of anti-HBV agents were not significantly different between the two groups ($p=0.222$).

Table 2. Treatment and HBV Reactivation during Follow-up

Variable	Total (n=60)	Within 1-week group (n=23)	After 1-week group (n=37)	p-value
Follow-up duration, median (IQR), mo	34 (20–74)	50 (31–86)	25 (17–70)	0.026
Duration from HBV treatment to initiation of biologics, median (IQR), day	32 (0–433)	0 (0–0)	387 (35–688)	<0.001
Antiviral agents, No. (%)				0.222
Entecavir	25 (41.7)	9 (39.1)	16 (43.2)	
Tenofovir	25 (41.7)	8 (34.8)	17 (45.9)	
Lamivudine	9 (15.0)	6 (26.1)	3 (8.1)	
Telbivudine	1 (1.7)	0	1 (2.7)	
Development of HBV reactivation, No. (%)	3 (5.0)	1 (4.3)	2 (5.4)	1.000

HBV, hepatitis B virus; IQR, interquartile range.

Table 3. Clinical Characteristics of the Three Patients with HBV Reactivation after Starting Biologics

Characteristics	Patient 1	Patient 2	Patient 3
Age, yr/sex	49/M	21/M	54/F
Time to initiation of biologics after initiating antiviral agent for HBV, day	433	696	0
Time to HBV reactivation after initiation of biologics, mo	7	25	8
Indication for biologics	RA	CD	RA
Biological agent	Anti-TNF- α agent (ETN)	Anti-TNF- α agent (ADA)	Anti-TNF- α agent (ADA)
Antiviral agent at baseline	Lamivudine	Tenofovir	Lamivudine
Concomitant steroids (dose)	None	None	Yes (10 mg)
Concomitant anti-inflammatory drugs	SSZ, HCQ	AZA	HCQ
HBV DNA titer (at anti-HBV agent initiation), IU/mL	2.2×10^7	7.5×10^7	5.6×10^5
Baseline laboratory findings (at biologics initiation)			
HBsAg/HBsAb	Positive/negative	Positive/negative	Positive/negative
HBeAg/HBeAb	Negative/negative	Positive/negative	Positive/negative
HBV DNA titer, IU/mL	2.5×10^4	1.1×10^3	5.6×10^5
ALT, IU/L	13	51	13
AST, IU/L	26	31	44
Total bilirubin, mg/dL	0.6	0.5	0.8
HBV DNA titer (lowest level), IU/mL	2.5×10^4	<15	2.2×10^3
At HBV reactivation laboratory findings			
HBV DNA titer, IU/mL	1.6×10^8	6.4×10^4	5.4×10^7
ALT, IU/L	30	523	54
AST, IU/L	38	384	61
Total bilirubin, mg/dL	0.9	0.7	1.0
Lamivudine resistance	Positive	Negative	Positive
Biologics stopped or interrupted due to HBV reactivation	Yes	No	No
Outcome	Recovered (lamivudine change to entecavir)	Recovered	Recovered (lamivudine change to adefovir)

HBV, hepatitis B virus; M, male; F, female; RA, rheumatoid arthritis; CD, Crohn's disease; TNF, tumor necrosis factor; ETN, etanercept; ADA, adalimumab; SSZ, sulfasalazine; HCQ, hydroxychloroquine; AZA, azathioprine; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Of the total of 60 patients, HBV reactivation occurred in three (5.0%). The crude rates of HBV reactivation did not significantly differ between the within 1-week group (n=1, 4.3%) and the after 1-week group (n=2, 5.4%) (p=1.000). Details of the clinical and laboratory characteristics of the three patients with HBV reactivation are shown in Table 3. The time to HBV reactivation after the initiation of biologics was 7 to 25 months. Two patients did not discontinue biologics, and one of them changed the anti-HBV agent from lamivudine to adefovir. All three patients recovered from HBV reactivation without long-term liver abnormalities.

3. Factors related to HBV reactivation

Next, we performed a Cox regression analysis to identify the factors associated with HBV reactivation in patients under treatment with biologics (Table 4). The results of this analysis showed that HBV reactivation was not significantly associated with age, sex, prednisolone dose, disease-modifying anti-rheumatic drug use, and high HBV DNA titer at baseline. Interestingly, the use of lamivudine was significantly associated with the risk of HBV reactivation (HR, 11.330; 95% CI, 1.026 to 125.059; p=0.048). Also, liver cirrhosis was significantly associated with the risk of

HBV reactivation (HR, 20.431; 95% CI, 1.756 to 237.775; $p=0.016$). In contrast, the initiation of biologics within 1 week of anti-HBV treatment was not significantly associated with the risk of HBV reactivation (HR, 0.657; 95% CI, 0.059 to 7.327; $p=0.733$). In addition, the Kaplan-Meier analysis showed that the cumulative probabilities of HBV reactivation did not significantly differ according to the timing of biologics initiation (≤ 1 week and >1 week) after anti-HBV therapy ($p=0.731$) (Fig. 1).

DISCUSSION

The present study showed HBV reactivation in patients with IMID under biologic treatments after anti-HBV therapy was not common, with a crude rate of 5% (3/60). Interestingly, we also found that early initiation (≤ 1 week) of biologics after starting anti-HBV agent was not significantly associated with a higher risk of HBV reactivation (HR, 0.657; 95% CI, 0.059 to 7.327; $p=0.733$).

HBV can persist inside the nucleus of hepatocytes for a long-time even if only trace amounts of HBV particles are present in the peripheral blood,⁶ and the natural course of HBV infection is determined by the interaction between the virus and host immune responses. Thus, suppression of host immunity by immunosuppressive therapy including anti-cancer drugs increases the risk of HBV reactivation.¹⁴ Furthermore, a high risk of HBV reactivation has been reported in patients with IMID with the introduction and widespread use of biologics such as anti-TNF- α agents.¹⁵⁻²⁰ Even though the rates of HBV reactivation were previously reported to be lower in patients receiving biologics than in those treating cancer chemotherapy,²¹ the rate of HBV reactivation has been reported to be up to 39%

in HBsAg-positive patients during treatment with anti-TNF- α agents.^{17,22} Anti-HBV treatment is beneficial for reducing the risk of HBV reactivation in patients receiving chemotherapy as well as in those exposed to biologics.^{17,23} The observed rate of HBV reactivation in our study (3/60, 5%) was similar to those reported from previous studies on HBsAg-positive patients with IMID receiving biologics and anti-HBV therapy.^{24,25}

Several HBV guidelines recommended that anti-HBV treatment should be initiated before starting biologics, including anti-TNF- α agents for patients with HBsAg.⁸⁻¹¹ However, the optimal timing for initiating biologics after anti-HBV therapy remains uncertain. Indeed, the guidelines do not specify the appropriate timing for starting the biologics after anti-HBV therapy.^{8,9,11} Although the American Association for the Study of Liver Diseases guideline mentions that anti-HBV agents should be administered

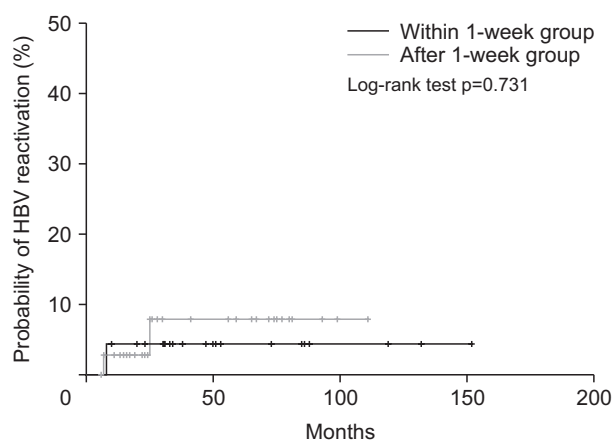


Fig. 1. Cumulative probability of hepatitis B virus (HBV) reactivation according to the time of initiation of biologics after HBV treatment.

Table 4. Univariate Cox Proportional Hazards Regression Analysis for the Risk of HBV Reactivation

Variable	HR (95% CI)	p-value
Biologics initiated within 1 week	0.657 (0.059–7.327)	0.733
Male sex	2.196 (0.199–24.250)	0.521
Age	0.946 (0.854–1.048)	0.286
IBD	0.575 (0.052–6.341)	0.651
Anti-TNF- α use	22.743 (0–NA)	0.747
Lamivudine use	11.330 (1.026–125.059)	0.048
Prednisolone dose	0.949 (0.790–1.136)	0.566
DMARDs use	3.581 (0.325–39.506)	0.298
Azathioprine use	2.961 (0.268–32.704)	0.376
HBV DNA ($>2,000$ IU/mL)	6.691 (0.604–74.105)	0.121
ALT	0.999 (0.963–1.037)	0.977
AST	1.011 (0.967–1.058)	0.629
Total bilirubin	4.069 (0.031–427.854)	0.572
Liver cirrhosis	20.431 (1.756–237.775)	0.016

HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; DMARDs, disease-modifying anti-rheumatic drugs; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not available.

7 days before the onset of anti-cancer drugs or immunosuppressants,¹⁰ the supporting evidence for this statement was very limited because of the lack of comparative study on the timing of biologics administration.²³ In our present study, one out of the 23 patients in the “within 1-week group” developed HBV reactivation, whereas two of the 37 patients in the “after 1-week group” developed HBV reactivation. In addition, results from the Cox regression and the Kaplan-Meier analysis showed that early initiation (<1 week) of biologics after anti-HBV therapy was not significantly associated with the risk of HBV reactivation (Table 4, Fig. 1). Interestingly, the majority (18/23, 78%) of patients in the “within 1-week group” initiated biologics and anti-HBV agents simultaneously, and only one of them experienced HBV reactivation during follow-up. These findings suggest that biologics may be initiated at any time within 1 week of commencing HBV treatment without increasing the risk of HBV reactivation.

Regarding the regimen of anti-HBV agents, most recent guidelines recommend tenofovir and entecavir as the first-line drug, whereas first-generation drugs such as lamivudine are not recommended as first-line treatment for patients with HBV because of high viral resistance to this drug.^{8-11,26} Several previous studies have shown that entecavir and tenofovir are more potent than lamivudine and have a higher genetic barrier to HBV resistance.^{21,23,27,28} It has also been shown that more than 60% of drug resistance occurs when lamivudine is used as an anti-HBV agent over 5 years.²⁹ There have been several reports of HBV reactivation due to resistance to lamivudine when it is used as an anti-HBV agent for chronic HBV infection.^{24,30,31} Similarly, in our study, two out of the three patients with HBV reactivation had been treated with lamivudine, and lamivudine resistance was confirmed as shown by HBV reverse transcriptase gene mutation analysis at the time of HBV reactivation. These two patients had decreased HBV DNA titers after changing to other anti-HBV agents (entecavir and adefovir) despite continuing the biologics. In addition, considering the results from the univariate analysis, it is likely that lamivudine use was associated with the increased risk of HBV reactivation. Additionally, underlying cirrhosis was present in the two patients for whom lamivudine resistance was confirmed. Liver cirrhosis is also a risk factor for HBV reactivation, particularly in association with immunosuppressive therapy.³²

In our study, only one of three patients with HBV reactivation discontinued biologics. The determination to discontinue or maintain biologics at HBV reactivation was based on the physician’s discretion. Indeed, there is no treatment guideline regarding how to use biologics upon or after HBV reactivation. Thus, further research inves-

tigating treatment strategies for use of biologics upon or after HBV reactivation are needed.

The present study had some limitations. First, this study may have been affected by selection bias inherent to its retrospective and single-center design. The retrospective nature of the study meant that HBV reactivation due to poor drug compliance could not be completely ruled out. Second, multivariable analysis could not be performed due to the small number of patients. Third, our study included patients who had already taken anti-HBV agents due to exacerbation of HBV, as well as those who had started antiviral therapy at the time of biologics initiation. Therefore, future studies are warranted that only include patients who have already started HBV treatment when they start biologics treatment or are expecting to start biologics treatment. Despite these limitations, this is the first study to compare the occurrence of HBV reactivation according to the time of biologics administration after the start of anti-HBV agents in patients with IMiD.

In conclusion, this study showed that the rate of HBV reactivation was not significantly different according to the timing of biologics administration after anti-HBV therapy. Thus, our results suggest that biologics may be initiated early (≤ 1 week) after anti-HBV therapy in HBsAg-positive patients with IMiD.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Study conception and design: S.M.A., S.H.P., S.H. Acquisition of data: S.M.A., J.C., B.D.Y., S.K.Y., J.S.O., Y.G.K., C.K.L., B.Y., S.H.P., S.H. Statistical analysis and interpretation of data: S.M.A., J.C., J.S.O., Y.G.K., C.K.L., B.Y., S.H.P., S.H. Drafting of the manuscript: S.M.A., S.H. Critical revision of the manuscript for important intellectual content: J.C., S.H.P., S.H.

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