



Has the COVID-19 Pandemic Affected HBsAg Seroclearance Rates in Chronic Hepatitis B Patients?

COVID-19 Pandemisi Kronik Hepatit B Hastalarında HBsAg Seroklirens Oranlarını Etkiledi mi?

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ABSTRACT

Objectives: The aim of this study is to document the increase in hepatitis B surface antigen (HBsAg) seroclearance that we observed during the coronavirus disease-2019 (COVID-19) pandemic.

Materials and Methods: Patients with chronic hepatitis B aged 18 years and older who were followed between 2010 and 2023 at three hospitals in Türkiye were included in this study. Rates of HBsAg seroclearance, seroconversion, and serological response among the patients were determined. Data from patients other than those who developed HBsAg seroclearance before the COVID-19 pandemic (before 2020) were analyzed.

Results: A total of 188 patients were included in the study. In total, 26 (13.8%) patients developed HBsAg seroclearance, 28 (15%) developed HBsAg seroconversion, and 21 (11.2%) developed a serological response. Of the patients who developed HBsAg seroclearance, 22 (84.6%) occurred in 2020 or later, and 4 (15.4%) occurred before 2020. The annual incidence rates of HBsAg seroclearance were 0.78% in 2014, 0.6% in 2017, 1.15% in 2019, 1.71% in 2020, 2.23% in 2021, 7.4% in 2022, and 1.2% in 2023. 95% of the patients were vaccinated with Pfizer-BioNTech and/or Sinovac-CoronaVac vaccines, and 36.4% had a COVID-19 infection.

Conclusion: In this study, the annual incidence rate of HBsAg seroclearance in the pre-pandemic period was consistent with the

ÖZ

Amaç: Bu çalışmanın amacı, koronavirüs hastalığı-2019 (COVID-19) pandemisi sırasında gözlemlediğimiz hepatit B yüzey antijeni (HBsAg) seroklirensindeki artışı belgelemektir.

Gereç ve Yöntemler: Bu çalışmaya, Türkiye'deki üç hastanede 2010-2023 yılları arasında takip edilen 18 yaş ve üzeri kronik hepatit B hastaları dahil edildi. Hastaların HBsAg seroklirens, HBsAg serokonversiyonu ve serolojik yanıt oranları belirlendi. COVID-19 pandemisi öncesi (2020 öncesi) HBsAg seroklirensi gelişen hastalar dışındaki hastaların verileri analiz edildi.

Bulgular: Çalışmaya toplam 188 hasta dahil edildi. Toplamda 26 (%13,8) hastada HBsAg seroklirensi, 28 hastada (%15) HBsAg serokonversiyonu ve 21 (%11,2) hastada serolojik yanıt gelişti. HBsAg seroklirensi gelişen hastaların 22'si (%84,6) 2020 ve sonrasında, 4'ü (%15,4) ise 2020 öncesi dönemdeydi. HBsAg seroklirensinin yıllık görülme oranları sırasıyla 2014'te %0,78, 2017'de %0,6, 2019'da %1,15, 2020'de %1,71, 2021'de %2,23, 2022'de %7,4 ve 2023'te %1,2 idi. Hastaların %95'i Pfizer-BioNTech ve/veya Sinovac-CoronaVac aşılarıyla aşılanmış ve %36,4'ünde COVID-19 enfeksiyonu tespit edilmiştir.

Sonuç: Bu çalışmada, pandemi öncesi dönemde HBsAg seroklirensinin yıllık görülme sıklığı literatürle tutarlıydı (%0-1,15), ancak bu oran

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literature (0-1.15%), but this rate tended to increase during the pandemic (7.4%). We suggest that this increase may be related to COVID-19 infection and vaccination.

Keywords: Hepatitis B, COVID-19, HBsAg seroclearance

pandemiyle birlikte artma eğilimindeydi (%7,4). Bu artışın nedenlerinin COVID-19 enfeksiyonu ve aşı ile ilgili olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Hepatit B, COVID-19, HBsAg seroklirnsi

Introduction

Hepatitis B virus (HBV) infection remains a significant global public health problem, causing substantial morbidity and mortality. All patients with chronic hepatitis B (CHB) have a high-risk of progression to cirrhosis and hepatocellular carcinoma (HCC). The main aim of treatment is to prevent the progression of the disease by suppressing HBV replication and to achieve the loss of hepatitis B surface antigen (HBsAg), which is the desired optimal end point (1,2). HBsAg can also be cleared from the patient's blood during the natural course of CHB. Loss of HBsAg can prevent disease progression to cirrhosis or HCC and increase the survival rate of affected patients (1,3). Factors such as age, gender, medication use, HBeAg (HBV e antigen, secreted dimeric protein) negativity, low HBV-DNA level and low HBsAg level are effective in HBsAg seroclearance and seroconversion (4,5). Spontaneous HBsAg seroclearance in patients with CHB infection varies by 0.5-1% per year (1,5,6).

Coronavirus disease-2019 (COVID-19) is a respiratory disease that can cause clinical manifestations of varying severity, ranging from upper respiratory tract infection to pneumonia, acute respiratory distress syndrome, and death. Although the main target of the new severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is the respiratory system, it can also affect other organs and systems such as the gastrointestinal system, hepatobiliary, cardiovascular, renal and central nervous systems (7). It also causes impairment of both acquired and innate immunity (8). It has also been reported in the literature that COVID-19 infection and vaccines cause reactivation of latent infections and opportunistic infections (9,10,11,12). Some studies (13,14) stated that the severity of disease and mortality rates were lower or that there was no difference in patients with CHB co-infection with COVID-19, while other studies (15,16,17) stated that co-infection caused a more severe clinical picture. Although many studies have investigated the relationship between COVID-19 and CHB co-infection, the association between these two infections has not been fully elucidated.

We observed an increase in HBsAg seroclearance among CHB patients who presented to our outpatient clinic after the coronavirus outbreak in 2019. We found no studies investigating whether COVID-19 infection affects HBsAg seroclearance. This study was conducted to document this observed increase.

Materials and Methods

Patients and Study Plan

This multicenter observational study was conducted in the infectious diseases and clinical microbiology units of two state hospitals and one university hospital located in different provinces of Türkiye.

Demographic data, comorbid diseases, HBV diagnosis date, treatments received and treatment durations, HBsAg seroclearance and seroconversion status and dates, and HBeAg and anti-HBe (serum antibodies against HBeAg) serological status for all patients were recorded on the prepared form. In addition, whether they had received the COVID-19 vaccine, which type and how many doses they had received, and whether they had a COVID-19 infection [confirmed by SARS-CoV-2 polymerase chain reaction (PCR)] were also examined. Patients who showed a serological response and did not have cirrhosis were followed for one year.

HBsAg seroclearance, seroconversion, and serological response rates among CHB patients followed in designated centers between 2010 and 2023 were determined. Data from patients other than patients who developed HBsAg seroclearance before the COVID-19 pandemic (before 2020) were analyzed. Patients who developed HBsAg seroclearance were not included in the evaluation the following year.

Inclusion Criteria

Patients with CHB aged 18 years or older who regularly attended follow-up appointments at these centers between 2010 and 2023 were included in the study.

Methods Used for Virological Markers

Serological tests were performed using a third-generation enzyme immunoassay for HBsAg, HBeAg, anti-HBe, and anti-HBs (Cobas; Roche, USA). HBsAg values were considered negative if between 0 and 1, and positive if >1. Anti-HBs values were considered negative if 0-10 and positive if >10. HBV-DNA level was measured by the real-time PCR (RT-PCR) method (Abbott real-time HBV; Abbott Laboratories, Germany). HBV-DNA levels below 10 IU/mL were considered negative.

Definitions

HBsAg seroclearance was defined as negative results in two consecutive serum samples, taken at least 6 months apart. HBsAg seroconversion was defined as the presence of anti-HBs antibodies (>10 IU/L) persisting for more than 6 months. The serological response to HBsAg is defined as HBsAg loss, i.e., HBsAg seroconversion (development of anti-HBs). Reduction of HBV-DNA to a level undetectable by PCR was defined as negativity (1,18,19).

Statistical Analysis

Descriptive statistics for all patients and for those who developed seroclearance after 2020 were evaluated using the SPSS 25.0 statistical package. Median (minimum-maximum) values were reported; the Shapiro-Wilk normality test was applied to continuous variables.

Ethics Committee Approval

The study protocol was approved by the Kafkas University Ethics Committee (decision no: 2022/03, date: 31.03.2022). . Due to the

retrospective nature of the study, the requirement for informed consent was waived by the Ethics Committee.

Results

A total of 188 patients were included in the study. Most patients (91%) were HBeAg seronegative, and the average follow-up period was 10 years. In total, HBsAg seroclearance was detected in 26 patients (13.8%), HBsAg seroconversion in 28 patients (15%), and a serological response in 21 patients (11.1%). Of the patients who developed HBsAg seroclearance, 22 (84.6%) were in 2020 and later, and four (15.4%) were in the period before 2020. The annual incidence rates of HBsAg seroclearance are 0.78% (1/128) in 2014, 0.6% (1/168) in 2017, 1.15% (2/174) in 2019, 1.71% (3/175) in 2020, 2.23% (4/179) in 2021, 7.4% (13/175) in 2022, and 1.2% (2/162) in 2023, respectively (Table 1). Figure 1 shows the distribution of HBsAg seroclearance rates by year.

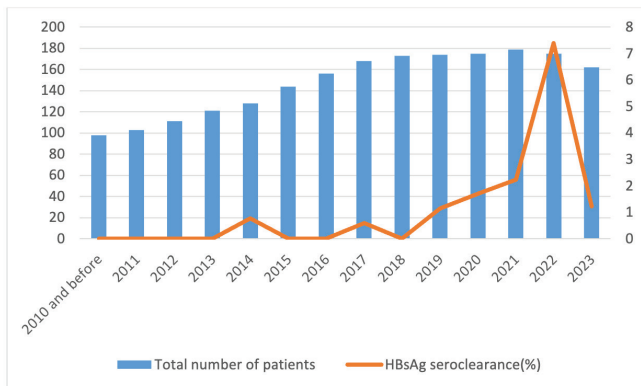


Figure 1. Distribution of HBsAg seroclearance rates by years
HBsAg: Hepatitis B surface antigen

Data from four patients whose HBsAg seroclearance occurred in the pre-pandemic period (before 2020) were not analyzed. Demographic data; comorbidities and treatment status; COVID-19 vaccination status and vaccine types; COVID-19 infection status; and other serological conditions for the remaining 184 patients and the 22 patients who developed HBsAg seroclearance in 2020 and later are presented in Table 2. The ages of the patients ranged from 25 to 88 years, with a median age of 53 years; most patients were male (59.8%). 46.7% of the patients had at least one comorbidity, and the three most common diseases were hypertension, diabetes mellitus, and cirrhosis (33.2%, 20.1%, and 6.5%, respectively). Most patients were HBeAg seronegative (90.7%) and anti-HBe positive (90.2%). Anti-HBs antibody was positive in 24 (13%) patients; a serological response to HBsAg was observed in 17 patients (9.2%); and anti-HBs antibody was detected in 7 (13.8%) patients despite HBsAg positivity (Table 2).

60.3% (n=111) of the patients had been receiving nucleos(t)ide treatment for an average of 60 months [of whom 64.8% (n=72) received tenofovir disoproxil, 28% (n=31) received entecavir, and 7.2% (n=8) received tenofovir alafenamide fumarate]. The final HBV-DNA level was negative in 69% of all patients. The treatment initiation date for 23.5% of patients was in 2020 or later (Table 2). Of the 111 patients treated, HBsAg seroclearance, HBsAg seroconversion, and serological response were detected in three (2.7%), three (2.7%), and two (1.8%) patients, respectively. HBsAg seroclearance was detected in 19 of 73 untreated patients (26%).

95% of patients had received at least one vaccine (Pfizer-BioNTech and/or Sinovac-CoronaVac). 53.3% received only Pfizer-BioNTech vaccines, 15.8% received only Sinovac-CoronaVac vaccines, and 26.1% received both Pfizer-BioNTech and Sinovac-CoronaVac vaccines. The average number of COVID-19 vaccine doses among the cases was 3. 36.4% of the cases had a COVID-19 infection, and 96.7% (n=178) had either received the COVID-19 vaccine or been infected (Table 2).

Table 1. Distribution of patients and HBsAg seroclearance rates by years

Years	Number of people followed (n)	HBsAg seroclearance (n)	Annual HBsAg seroclearance rate (per 100 persons/year)
2010	98	0	0
2011	103	0	0
2012	111	0	0
2013	121	0	0
2014	128	1	0.78
2015	144	0	0
2016	156	0	0
2017	168	1	0.6
2018	173	0	0
2019	174	2	1.15
2020	175	3	1.71
2021	179	4	2.23
2022	175	13	7.42
2023	164	2	1.21

HBsAg: Hepatitis B surface antigen

Table 2. Basic characteristics, COVID-19 vaccination and infection status, and other serological conditions of 184 patients and 22 patients who developed HBsAg seroclearance in 2020 and later

Variables	Total n=184 (%)	HBsAg seroclearance (2020 and later) n=22 (%)
Age median (min-max)	53 (25-88)	54 (32-72)
Male gender	110 (59.8)	18 (81.8)
Comorbidity	86 (46.7)	14 (63.6)
Hypertension	61 (33.2)	13 (59.1)
Diabetes mellitus	37 (20.1)	6 (27.3)
Cirrhosis	12 (6.5)	1 (4.5)
Anti-HBs-positive status	24 (13)	17 (77.3)
HBsAg/anti-HBs double positive	7 (3.8)	-
Serological response for HBsAg	17 (9.2)	17 (77.3)
HBeAg-negative status	167 (90.7)	22 (100.0)
Anti HBe-positive status	166 (90.2)	22 (100.0)
Nucleoside(t)id treatment	111 (60.3)	3 (13.6)
Tenofovir disoproxil	72 (64.8)	3 (100)
Entecavir	31 (28)	0 (0)
Tenofovir alafenamide fumarate	8 (7.2)	0 (0)
Tenofovir treatment duration (month)	60 (1-156)	108 (36-120)
Entecavir treatment duration (month)	48 (3-180)	0
Tenofovir alafenamide fumarate (month)	24 (10-48)	0
HBV-DNA negative	127 (69%)*	21 (95.4)*
COVID-19 vaccine	175 (95%)	20 (91%)
Pfizer-BioNTech	98 (53.3)	12 (54.5)
Sinovac-CoronaVac	29 (15.8)	1 (4.5)
Pfizer-BioNTech and Sinovac-CoronaVac	48 (26.1)	7 (31.8)
Having COVID-19 infection	67 (36.4)	8 (36.4)
Vaccinated or infected with COVID-19	178 (96.7)	22 (100.0)
Total COVID-19 vaccination dose (mean)	3 (1-5)	3 (1-5)
Pfizer-BioNTech vaccine dose (mean)	2 (1-4)	2 (1-3)
Sinovac-CoronaVac vaccine dose (mean)	2 (1-5)	2 (2-5)

* The last value measured at the time inclusion in the study
 * The value measured at the time HBsAg seroclearance developed. HBsAg: Hepatitis B surface antigen, COVID-19: Coronavirus disease-2019, HBV: Hepatitis B virus

Among 178 patients who contracted COVID-19 infection and/or were vaccinated during the pandemic, HBsAg seroclearance was detected in 22 (12.3%), HBsAg seroconversion in 22 (12.3%), and serological response in 17 (9.5%). Of the six patients who had not had a COVID-19 infection or had not been vaccinated during the pandemic, none showed HBsAg serological responses. HBsAg seroconversion was detected in two (33.3%) patients.

Discussion

In CHB, HBsAg seroclearance and seroconversion are important events in controlling the disease and preventing complications and constitute the main goal of treatment (5). In this study, annual HBsAg seroclearance rates increased during the pandemic period and peaked in 2022 (7.4%); the 10-year cumulative incidence rate of HBsAg seroclearance was 13.8% (Figure 1).

The main goal of treatment for CHB is to achieve HBsAg loss, which is the optimal endpoint. Spontaneous HBsAg loss may also occur over the long term in patients who do not receive treatment. Spontaneous HBsAg seroclearance is rare, with an incidence of only 1.5. Kobayashi et al. (4) found annual HBsAg seroclearance rates as 1.65% in the patient group not receiving treatment and 2.05% in the patient group receiving treatment. It is reported that the annual seroclearance rates of HBsAg are 2.4% in China (20), 1.15% in Taiwan (21), and 0.5% in Alaska (22). Additionally, an analysis reported that annual HBsAg seroclearance rates were between 0.5% and 1% (5). Türkiye is a moderately endemic region (4%) in terms of CHB and the dominant genotype is D (23). In this study, the annual incidence rate of HBsAg seroclearance was 0-1.15% in the pre-pandemic period, consistent with the literature; however, during the pandemic this rate showed an increasing trend and was found to be 7.4% in 2022 (Figure 1, Table 1). In a systematic review where the cumulative

incidence rates of HBsAg seroclearance were evaluated, the 10-year cumulative incidence rate was reported to be 8.16% (95% confidence interval, 5.24-11.72) in 12 studies analyzed (24). In this study, the 10-year cumulative incidence rate of HBsAg seroclearance (13.8%) was significantly higher than previously reported values. Differences in seroclearance rates of HBsAg by country may be related to variation in HBV genotypes and treatment conditions. Additionally, previous studies have found that factors such as age (≥ 50 years), gender (male), medication use, HBeAg negativity, low HBV-DNA level and low HBsAg level are effective in HBsAg seroclearance (4,5,24). In this study, most (81.8%) of the patients who developed HBsAg seroclearance were male; their median age was 54 years; all (100%) were HBeAg negative; and only three (13.6%) patients were receiving nucleos(t)ide therapy. HBV-DNA levels were negative in all but one patient at the time of seroclearance (Table 2).

In the study by Masrou-Roudsari et al. (19), the HBsAg seroconversion rate was found to be 5.5% and the serological response rate was 5% at an average follow-up of 15 years. In our study, at an average follow-up of 10 years, the HBsAg seroconversion and serological response rates were higher than those reported in the literature, at 13% and 9.2%, respectively.

Previous studies have reported that even in HBeAg-negative patients treated with nucleos(t)ide analogs for many years, HBsAg seroclearance and seroconversion rates are low and these rates are not related to treatment history (4,6,19,24). In the study conducted by Masrou-Roudsari et al. (19), HBsAg seroclearance was observed in 2.6% of the treated patients and HBsAg seroconversion in 2.6% of the treated patients during a 15-year follow-up. In our study, HBsAg seroclearance and HBsAg seroconversion were each observed in 2.7% of the treated patients during a 10-year follow-up.

In this study, although the factors affecting HBsAg seroclearance were similar to those previously reported, the annual and cumulative HBsAg seroclearance rates after the COVID-19 pandemic were significantly higher than those in the pre-pandemic period. However, we could not determine the reasons for this increase. In our study, all patients who developed post-pandemic seroclearance were either vaccinated against COVID-19 or had a COVID-19 infection, and 86.3% of the patients had received an average of two doses of the mRNA (Pfizer-BioNTech) vaccine (Table 2). While there are many studies investigating the relationship between COVID-19 infection and vaccines and CHB (25,26,27) in the literature, the interaction between these two infections and how the COVID-19 pandemic affected the course of hepatitis B infection remains unclear.

Study Limitation

Our study had some limitations. Statistical analysis could not be performed because the number of patients was small and most patients had either received the COVID-19 vaccine or had been infected with COVID-19. In addition, due to excessive strain on the healthcare system during the COVID-19 pandemic, routine check-ups of CHB patients were disrupted, and the course of the patients' biochemical parameters during this period could not be followed.

Conclusion

Although the reasons were not identified in this study, we found a significant increase in HBsAg seroclearance during the COVID-19 pandemic. We believe that this significant increase in HBsAg seroclearance during the pandemic should be investigated in more comprehensive studies.

Ethics

Ethics Committee Approval: The study protocol was approved by the Kafkas University Ethics Committee (decision no: 2022/03, date: 31.03.2022).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived by the Ethics Committee.

Footnotes

Authorship Contributions

Concept: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Design: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Data Collection or Processing: N.M., S.T., B.B.S., Analysis or Interpretation: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Literature Search: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Writing: N.M., F.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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