

Are nucleos(t)ide analogues effective against severe outcomes in COVID-19 and hepatitis B virus coinfection?

Gupse Adali¹, Pinar Gokcen¹, Fatih Guzelbulut², Ayca Gokcen Degirmenci Salturk², Nihat Bugra Agaoglu³, Busra Unal⁴, Levent Doganay^{4,5}, Kamil Ozdil¹

¹Department of Gastroenterology, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey; ²Department of Gastroenterology, University of Health Sciences Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey; ³GLAB (Genomic Laboratory), University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey; ⁴Department of Gastroenterology, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey; ⁵GLAB (Genomic Laboratory), University of Health Sciences Umraniye Training and Research Hospital Istanbul, Turkey

Abstract

Background and Aim: The impact of chronic hepatitis B virus (HBV) infection and nucleos(t)ide analogue (NUC) treatment on disease severity and clinical outcomes in patients with coronavirus 2019 (COVID-19) is unknown. The objective of this study was to determine whether HBV infection and the use of NUCs impacts mortality in patients with COVID-19.

Materials and Methods: A total of 231 adult patients (77 with COVID-19 and HBV coinfection) with a laboratory-confirmed diagnosis of COVID-19 were enrolled in this retrospective study. Univariate and binary logistic regression analysis were performed to evaluate the risk factors for mortality from COVID-19.

Results: Patients with COVID-19 and HBV coinfection had a similar rate of mortality to those without HBV coinfection (7.8% vs 9.7%; $p=0.627$). Cardiovascular disease (odds ratio [OR]: 8.22, 95% confidence interval [CI]: 1.52-44.2; $p=0.014$) and a high basal aspartate transaminase level (OR: 7.94, 95% CI: 1.81-34.8; $p=0.006$) were independent predictors of mortality due to COVID-19. In the COVID-19 and HBV coinfection group, the patients who died had a significantly higher median level of HBV DNA than patients who survived (378 IU/mL vs 0 IU/mL; $p=0.048$). Thirty (39%) patients with HBV coinfection received NUC treatment, and none of these patients died.

Conclusion: HBV infection was not associated with mortality in patients with COVID-19, and it seems that NUC treatment for HBV infection might have an antiviral effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Keywords: Chronic HBV infection; chronic hepatitis; cirrhosis; COVID-19; hepatitis B; nucleos(t)ide analogue treatment.

How to cite this article: Adali G, Gokcen P, Guzelbulut F, Degirmenci Salturk AG, Agaoglu NB, Unal B, et al. Are nucleos(t)ide analogues effective against severe outcomes in COVID-19 and hepatitis B virus coinfection? *Hepatology Forum* 2021; 2(3):91-96.

Received: June 13, 2021; **Accepted:** August 02, 2021; **Available online:** September 15, 2021

Corresponding author: Gupse Adali; Saglik Bilimleri Universitesi, Umraniye Egitim ve Arastirma Hastanesi, Gastroenteroloji Anabilim Dalı, Istanbul, Turkey
Phone: +90 216 632 18 18; **e-mail:** gupseadali@gmail.com

 OPEN ACCESS
This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

© Copyright 2021 by Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, emerged in Wuhan, China, in December 2019. In addition to respiratory disorders, SARS-CoV-2 can also cause liver damage.^[1,2] The incidence of elevated liver function in patients with COVID-19 ranges between 14% and 83%.^[2,3] Liver injury occurs more commonly in patients with severe COVID-19, and patients with elevated liver biochemistry findings are at increased risk of death.^[4]

Evidence shows that patients with chronic liver disease, especially cirrhosis, may be at higher risk of death from COVID-19.^[5,6] The World Health Organization (WHO) estimates that 3.5% of the population worldwide lives with chronic hepatitis B virus (HBV) infection.^[7] The overall hepatitis B surface antigen seropositivity is 4% in Turkey.^[8] Although SARS-CoV-2 and HBV can both cause abnormal liver function, it is not clear whether HBV infection has an impact on the outcomes of COVID-19. Recent studies have suggested that nucleos(t)ide analogues (NUCs) used to treat HBV infection may have an antiviral effect on SARS-CoV-2.^[9,10] This study was designed to evaluate whether HBV infection and the use of NUCs had an impact on mortality in patients with COVID-19.

Materials and Methods

This study was approved by the Turkish Ministry of Health and by the ethics committees of Umraniye Training and Research Hospital and Haydarpaşa Numune Training and Research Hospital on May 12, 2020 (no: 151). Informed patient consent was not required for this study because the analysis used anonymous clinical data that were obtained after each patient provided written consent for treatment.

Study Population

The records of all adult patients (age >18 years) who had been admitted to 2 Istanbul tertiary district hospitals (University of Health Sciences Istanbul Umraniye Training and Research Hospital and Haydarpaşa Numune Training and Research Hospital) and tested positive for SARS-CoV-2 RNA (nasopharyngeal and oropharyngeal) according to a reverse transcription-polymerase chain reaction (RT-PCR) assessment ($n=349$) between March 11, 2020, and June 30, 2020 were retrospectively analyzed. Patients who had not been tested for the hepatitis B surface antigen, hepatitis C antibody, or the HIV

antibody, were excluded (n=118). Patients with clinical, laboratory, or radiological findings suggestive of cirrhosis were excluded if the underlying etiology was not HBV infection, as the aim of this research was to assess the impact of HBV infection on COVID-19. After applying the exclusion criteria, 154 patients without chronic liver disease and 77 patients with HBV infection who were positive for SARS-CoV-2 RNA (nasopharyngeal and oropharyngeal) according to RT-PCR testing were included in this study.

Patient Management and Variables

Diagnosis and management of all of the patients was performed according to the Directorate General of Public Health Guidelines issued by the Turkish Ministry of Health.^[11] All of the patient samples were analyzed for SARS-CoV-2 RNA (nasopharyngeal and oropharyngeal) via RT-PCR at an accredited laboratory. All of the patients with confirmed COVID-19 started their treatment as inpatients, and after the initial assessment of disease severity, they were either discharged or continued their treatment in the hospital. Treatment was initiated with hydroxychloroquine and/or azithromycin in all cases. Favipiravir (a 3200-mg loading dose and 1200-mg maintenance dose) was administered for 5 days to patients who did not improve after receiving the initial treatment. Additionally, anti-interleukin 6 (IL-6) therapy (tocilizumab) or convalescent plasma was used if deemed appropriate. All of the patients were followed up 1 month after discharge at outpatient clinics.

Baseline laboratory values and demographic, clinical, length-of-stay, and intensive care unit admission data were collected from electronic medical records. Body mass index values were recorded as obese (≥ 30 kg/m²) or nonobese (< 30 kg/m²), according to WHO definitions.^[11] The diagnosis of cirrhosis was made based on clinical, laboratory, radiological, and endoscopic findings. Among the 14 cirrhosis patients, 9 had Child-Pugh Class A cirrhosis, 3 had Child-Pugh Class B cirrhosis, and 2 had Child-Pugh Class C cirrhosis. Genotype D is the dominant HBV genotype in Turkey in all age groups; therefore, no genotype analysis was performed. Of the 77 HBV-positive patients, 5 (6.5%) were hepatitis B e antigen-positive, and 3 (3.9%) were anti-delta-positive. The HBV DNA level, liver fibrosis stage (according to the Ishak scoring system), and NUC treatment details were recorded for the patients with HBV infection. The HBV DNA levels of the previous 6 months were available for 50 (65%) patients. Liver fibrosis stage data were available for 38 (49%) patients who had HBV infection without cirrhosis (n=63) and 31 (40%) patients had significant fibrosis ($\geq F2$). The available treatment information for all of the study patients indicated that 47 (61%) did not receive NUC treatment, 8 (10.4%) were given entecavir, 18 (23.4%) received tenofovir disoproxil fumarate, and tenofovir alafenamide was administered to 4 (5.2%) patients. The electronic medical records were also reviewed for prior abdominal imaging results.

Statistical Analysis

Continuous variables are presented as the median and interquartile range, and categorical variables are presented as percentages and frequencies. A 2-tailed p value of < 0.05 was considered significant. Univariable analyses to identify variables associated with patient outcome (alive/dead) due to COVID-19 were investigated using a chi-squared, Fisher exact, or Mann-Whitney U-test, as appropriate. Multivariable analysis was used to investigate factors identified in

the univariate analyses using logistic regression analysis to determine independent predictors of patient outcome. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess model fit. A 5% type-I error level was established as an indication of statistical significance. All of the data were analyzed using the IBM SPSS Statistics for Windows, Version 24.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 231 patients who had a confirmed COVID-19 infection, 77 of whom had HBV coinfection (n=77; 14 cirrhotic, 63 noncirrhotic) and 154 who did not have HBV coinfection, were included in this study. Patients without HBV coinfection had a significantly longer hospital stay than patients with HBV coinfection (10 days vs 7 days; $p=0.000$), and these patients more frequently received hydroxychloroquine, azithromycin, or anti-IL6 treatment. There were no significant differences between the groups in terms of age, sex, comorbidities, or mortality rate. Death occurred in 21 patients (9%) of the total cohort. The clinical characteristics of COVID-19 patients with and without HBV coinfection are summarized in Table 1.

In patients with HBV coinfection, the median HBV DNA level was significantly higher in patients who died than in those who survived (378 IU/mL vs 0 IU/mL; $p=0.048$). Factors associated with death in univariate analysis were age (≥ 65 years); cardiovascular disease; baseline creatinine, aspartate transaminase (AST), alanine transaminase (ALT), and albumin levels; and treatment with anti-IL6 (tocilizumab), convalescent plasma, or favipiravir. An elevated AST level (≥ 35 U/L) was significant. HBV coinfection and cirrhosis were not associated with death. Thirty of 77 patients with HBV coinfection received NUC treatment, and none of them died ($p=0.085$). Multivariate analysis of factors associated with death demonstrated that cardiovascular disease and a baseline AST higher than 35 U/L were significant (Table 2).

Patients with COVID-19 and HBV coinfection with cirrhosis had a similar mortality rate to those without cirrhosis (14.3% vs 6.3%; $p=0.298$). The proportion of patients with cirrhosis who received NUC treatment was significantly higher than those without cirrhosis (78.6% vs 30.2%; $p=0.001$). The median age of patients with cirrhosis was higher than that of those without cirrhosis (61 years vs 56 years; $p=0.041$). Patients with cirrhosis had a higher median total bilirubin and prothrombin level than those without cirrhosis (0.71 vs 0.47 mg/dL; $p=0.001$ and 15.9 vs 14 seconds; $p=0.001$, respectively). Hepatocellular carcinoma was more frequent in patients with cirrhosis than those without cirrhosis (14.3% vs 0%; $p=0.031$) (Table 3).

No significant drug-drug interaction or serious drug-induced liver injury was recorded during the hospitalization period.

Discussion

The clinical data of the outcomes of COVID-19 patients with chronic HBV infection suggests that HBV infection did not increase the mortality risk in most cases. We analyzed 231 patients with COVID-19, of whom 77 patients had HBV coinfection. Our results indicated that patients with HBV coinfection had a similar COVID-19 mortality rate to patients without HBV coinfection (7.8% vs 9.7%). Patients with HBV coinfection and cirrhosis had a similar mortality rate to those without cirrhosis (14.3% vs. 6.3%). Most importantly, none of the 30 patients who received NUC treatment for HBV infection died, and the median HBV DNA level was significantly lower in patients who survived.

Table 1. Clinical characteristics of COVID-19 patients with and without HBV coinfection

	HBV (n=77)	Non-HBV (n=154)	p
Age (years)	57.5 (28–93)	53 (19–91)	0.148
Sex (male)	48 (62.3)	105 (68.2)	0.376
Smoker	7 (9.1)	9 (5.8)	0.360
Obesity (BMI \geq 30 kg/m ²)	12 (16)	21 (13.6)	0.633
Cardiovascular disease	3 (3.9)	16 (10.4)	0.090
Diabetes mellitus	16 (20.8)	33 (21.4)	0.909
Hypertension	18 (23.4)	54 (35.1)	0.071
COPD	6 (7.8)	16 (10.4)	0.526
Non-HCC cancer	3 (3.9)	3 (1.9)	0.403
HCC	2 (2.6)	0 (0)	0.110
Liver fibrosis stage*			
F 0–1	7 (9)	–	
F 2–4	17 (22)	–	
Cirrhosis	14 (18.1)	–	
Child–Pugh A	9 (11.7)	–	
Child–Pugh B	3 (3.9)	–	
Child–Pugh C	2 (2.6)	–	
MELD score	11 (7–23)	–	
NUC treatment	30 (39)	–	
HBV DNA [†] (IU/mL)	0 (0–6368853)	–	
Creatinine (mg/dL)	0.85 (0.53–8.27)	0.93 (0.52–6.66)	0.074
ALT (U/L)	31 (5–536)	30 (8–712)	0.279
AST (U/L)	32 (13–264)	34 (11–822)	0.100
Total bilirubin (mg/dL)	0.54 (0.13–14.93)	0.56 (0.14–4.2)	0.840
Albumin (g/dL)	3.95 (2.1–4.6)	3.91 (2.36–4.93)	0.243
Prothrombin time (s)	14.2 (12.1–28.4)	14.3 (12.2–48.6)	0.929
Hydroxychloroquine	55 (71.4)	153 (99.4)	0.000
Azithromycin	38 (49.4)	146 (94.8)	0.000
Anti-IL6 therapy	1 (1.3)	13 (8.4)	0.039
Convalescent plasma	0 (0)	5 (3.2)	0.172
Favipiravir	28 (36.4)	66 (42.9)	0.344
Hospital stay (days)	7 (0–34)	10 (1–106)	0.000
Death	6 (7.8)	15 (9.7)	0.627

Data are shown as median (interquartile range) or n (%). *: Liver fibrosis stage (Ishak) was available for 38 patients. †: HBV DNA was available for 50 patients. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus 2019; F: Fibrosis; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; IL: Interleukin; MELD: Model for end-stage liver disease; NUC: Nucleos(t)ide analogue.

Zou et al.^[12] analyzed 105 patients with COVID-19 and HBV coinfection; 13.3% of this group had liver injury, and 6.67% died. A multicenter study from the United States analyzed 867 patients with chronic liver disease and COVID-19. Sixty-two of these patients had HBV, and 4.1% of the HBV patients died. HBV was not associated with mortality in either univariable or multivariable analyses.^[13] Chen et al.^[14] compared 20 patients with HBV and COVID-19 coinfection and 306 patients with COVID-19 without HBV. None of the patients with HBV died, and they concluded that HBV infection had no effect on COVID-19 mortality. Wu et al.^[15] analyzed 70 patients with HBV and COVID-19 coinfection, and none of these patients died. The lower mortality rates in other studies may have been due to the smaller percentage of patients with HBV cirrhosis than in our

study. We observed that the patients who died had a significantly higher median level of HBV DNA than the patients who survived (378 IU/mL vs 0 IU/mL; $p=0.048$). Therefore, another reason for the higher mortality rate could be the greater frequency of detectable HBV DNA levels in our study; however, the above studies did not provide HBV DNA levels.

Chen et al.^[16] analyzed 15 patients with HBV and COVID-19, and 2 (13.3%) died. In a multicenter research network study, 12% mortality was observed among 250 patients with pre-existing liver disease (10 patients with HBV).^[17] Marjot et al.^[5] noted that among 745 patients with both COVID-19 and chronic liver disease from 2 international reporting registries, 92 had HBV ($n=37$, 40% with HBV cirrhosis),

Table 2. Clinical characteristics of COVID-19 patients and factors associated with death

	Survived n=210	Died n=21	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p	OR (95% CI)	p
Age (years)	51 (18–91)	66 (28–93)	0.92 (0.89–0.96)	0.000		
Age ≥65 years	37 (17.6)	12 (57.1)	6.23 (2.44–15.8)	0.000	1.92 (0.54–6.79)	0.310
Sex (male)	137 (65.2)	16 (76.2)	1.70 (0.60–4.84)	0.312		
Smoker	16 (7.6)	0 (0)	0.90 (0.86–0.94)	0.373		
Obesity (BMI ≥30 kg/m ²)	32 (15.4)	1 (4.8)	3.63 (0.47–28.0)	0.325		
Cardiovascular disease	13 (6.2)	6 (28.6)	6.06 (2.01–18.2)	0.001	8.22 (1.52–44.2)	0.014
Diabetes mellitus	44 (21)	5 (23.8)	1.17 (0.40–3.39)	0.760		
Hypertension	62 (29.5)	10 (47.6)	2.17 (0.87–5.37)	0.094		
COPD	21 (10)	1 (4.8)	2.22 (0.28–17.4)	0.447		
Non-HCC cancer	4 (1.9)	2 (9.5)	5.42 (0.93–31.5)	0.060		
HCC	2 (1)	0 (0)	0.90 (0.87–0.94)	0.999		
HBV infection	71 (33.8)	6 (28.6)	1.27 (0.47–3.43)	0.627	1.68 (0.48–5.89)	0.414
Cirrhosis	12 (5.7)	2 (9.5)	1.73 (0.36–8.34)	0.490		
NUC treatment	30 (14.2)	0 (0)	0.89 (0.85–0.93)	0.085		
Creatinine (mg/dL)	0.86 (0.52–8.27)	1.18 (0.75–2.82)	0.58 (0.36–0.94)	0.028	0.65 (0.4–5.89)	0.091
ALT (U/L)	29 (5–536)	39 (11–712)	0.99 (0.98–0.99)	0.026		
AST (U/L)	31.5 (11–264)	45 (14–822)	0.98 (0.97–0.99)	0.006		
AST ≥35 (U/L)	76 (38)	15 (71.4)	4.07 (1.51–10.9)	0.005	7.94 (1.81–34.8)	0.006
Total bilirubin (mg/dL)	0.54 (0.13–14.9)	0.64 (0.14–4.2)	0.90 (0.68–1.21)	0.510		
Albumin (g/dL)	3.98 (2.36–4.93)	3.42 (2.1–4.41)	5.58 (2.3–13.55)	0.000	2.99 (0.97–9.2)	0.056
Prothrombin time (s)	14.1 (12.1–42.1)	17.3 (13.1–48.6)	0.99 (0.97–1.01)	0.487		
Hydroxychloroquine	188 (89.5)	20 (95.2)	2.34 (0.29–18.2)	0.418		
Azithromycin	164 (78.1)	20 (95.2)	5.61 (0.73–42.9)	0.097		
Anti-IL6 therapy	10 (4.8)	4 (19)	4.7 (1.33–16.6)	0.016		
Convalescent plasma	3 (1.4)	2 (9.5)	7.26 (1.14–46.1)	0.036		
Favipiravir	77 (36.7)	17 (81)	7.34 (2.38–22.6)	0.001	2.82 (0.76–10.4)	0.120
Hospital stay (days)	8 (0–106)	10 (4–53)	0.97 (0.94–1.0)	0.090		

Data are shown as median (interquartile range) or n (%). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus 2019; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; IL: Interleukin; NUC: Nucleos(t)ide analogue.

and 15.3% of the HBV patients died. The mortality in patients with chronic liver disease without and with cirrhosis was 8% and 32%, respectively. According to their multivariable analysis, HBV was not associated with mortality. Our mortality rate in patients with HBV and COVID-19 coinfection was 7.8%, and most of these patients were noncirrhotic (82%), with various degrees of liver fibrosis. Most of the patients with HBV cirrhosis and COVID-19 coinfection had Child-Pugh A cirrhosis (n=9, 64%), and the rate of mortality among patients with cirrhosis was 14.3%. The low mortality of cirrhotic patients in our study in comparison with the observations of Marjot et al.^[5] could be attributed to the small number of patients with decompensated cirrhosis. Consistent with other studies, we found no association between HBV and COVID-19 mortality. Cardiovascular disease and a high basal AST level were independent predictors of mortality, a finding that was also reported in a recently published meta-analysis of 34 studies.

COVID-19 incidence and outcomes in patients with HBV receiving NUC treatment have not been addressed in detail. However, recent studies have demonstrated that tenofovir and entecavir inhibit SARS-

CoV-2 RNA-dependent RNA polymerase. Thus, NUCs may have a role as potential COVID-19 therapeutics.^[10,18,19] Lens et al.^[20] published a large cohort study conducted in Spain, and of 1764 HBV patients who were receiving tenofovir, only 8 patients (0.4%) had COVID-19 and none died. Additionally, a multicenter study from China that included 70 patients with HBV and a COVID-19 coinfection reported that the majority of patients were on HBV antiviral treatment and that all of the patients recovered.^[15] In our study, HBV antiviral treatment data were available for all of the HBV-coinfected patients; in all, 30 patients were on NUC treatment: 22 were receiving tenofovir and 8 were receiving entecavir. Of those 30 patients, 24 had undetectable HBV DNA on admission, and none died. These results suggest that NUCs may have a positive effect on the outcome of COVID-19.

This study included a relatively small number of patients. The potential bias regarding the selection of patients with symptoms who were admitted to the hospital prevents us from drawing any conclusions about the incidence of COVID-19 and the effects of NUCs in this cohort. However, our findings in the 77 patients with HBV and a COVID-19 coinfection represent a detailed assessment of clinical

Table 3. Clinical characteristics of patients with COVID-19 and HBV with and without cirrhosis

	HBV without cirrhosis n=63	HBV with cirrhosis n=14	p
Age (years)	56 (28–93)	61 (34–80)	0.041
Age ≥65	9 (14.3)	5 (35.7)	0.117
Sex (male)	37 (58.7)	11 (78.6)	0.166
Smoker	4 (6.3)	3 (21.4)	0.108
Obesity (BMI ≥30 kg/m ²)	9 (14.8)	3 (21.4)	0.686
Cardiovascular disease	2 (3.2)	1 (7.1)	0.457
Diabetes mellitus	13 (20.6)	3 (21.4)	0.947
Hypertension	16 (25.4)	2 (14.3)	0.499
COPD	5 (7.9)	1 (7.1)	0.920
Non-HCC cancer	1 (1.6)	2 (14.3)	0.083
HCC	0 (0)	2 (14.3)	0.031
Creatinine (mg/dL)	0.88 (0.53–8.27)	0.8 (0.56–1.18)	0.294
ALT (U/L)	32 (8–536)	22 (5–116)	0.906
AST (U/L)	28 (13–250)	38 (14–264)	0.055
AST ≥35 (U/L)	17 (31.5)	8 (61.5)	0.059
Total bilirubin (mg/dL)	0.47 (0.13–1.22)	0.71 (0.46–14.93)	0.001
Albumin (g/dL)	3.99 (2.86–4.58)	3.57 (2.1–4.6)	0.077
Prothrombin time (s)	14 (12.1–23.7)	15.9 (14–28.4)	0.001
HBV DNA (IU/mL)*	0 (0–6368853)	0 (0–6700)	0.621
NUC treatment	19 (30.2)	11 (78.6)	0.001
Hydroxychloroquine	46 (73)	9 (64.3)	0.526
Azithromycin	32 (50.8)	6 (42.9)	0.591
Anti-IL6 therapy	1 (1.6)	0 (0)	1.000
Favipiravir	20 (31.7)	8 (57.1)	0.074
Hospital stay (days)	6 (0–15)	10 (4–34)	0.152
Death	4 (6.3)	2 (14.3)	0.298

Data are shown as median (interquartile range) or n (%). *: HBV DNA was available for 50 patients; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus 2019; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; IL: Interleukin; NUC: Nucleos(t)ide analogue.

variables regarding HBV. To our knowledge, it is the largest such cohort to date, including 30 patients receiving NUC treatment with HBV and a COVID-19 coinfection.

Conclusion

HBV infection does not appear to increase the mortality of COVID-19, and antiviral treatments for HBV infection (tenofovir and entecavir) might have an antiviral effect on SARS-CoV-2 infection.

Ethics Committee Approval: The Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 12.05.2020, number: 151).

Peer-review: Externally peer-reviewed.

Author Contributions: Adali G, design of the study, analysis, and interpretation of the data, and drafting the paper; Gokcen P, Agaoglu NB, Unal B and Degirmenci Salturk AG acquisition of data for the manuscript; Doganay L, Ozdil K, revising the manuscript critically for important intellectual content; Guzelbulut F, acquisition of data for the manuscript and revising it critically for important intellectual content.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507-513.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708-1720. [CrossRef]
- Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal liver tests in COVID-19: A retrospective observational cohort study of 1,827 patients in a major U.S. hospital network. *Hepatology* 2020;72(4):1169-1176. [CrossRef]
- Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020;52(4):584-599. [CrossRef]
- Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol*. 2021;74(3):567-577. [CrossRef]

6. Sarin SK, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, et al; APASL COVID Task Force, APASL COVID Liver Injury Spectrum Study (APCOLIS Study-NCT 04345640). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatology* 2020;14(5):690-700. [\[CrossRef\]](#)
7. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available from: <https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/>. Accessed on May 25, 2021.
8. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. *Clin Microbiol Infect* 2015;21(11):1020-1026. [\[CrossRef\]](#)
9. Jockusch S, Tao C, Li X, Anderson TK, Chien M, Kumar S, et al. A library of nucleotide analogues terminate RNA synthesis catalyzed by polymerases of coronaviruses that cause SARS and COVID-19. *Antiviral Res* 2020;180:104857. [\[CrossRef\]](#)
10. Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sci* 2020;253:117592. [\[CrossRef\]](#)
11. Obesity and overweight World Health Organization Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed on May 25, 2021.
12. Zou X, Fang M, Li S, Wu L, Gao B, Gao H, et al. Characteristics of liver function in patients with SARS-CoV-2 and chronic HBV coinfection. *Clin Gastroenterol Hepatol* 2021;19(3):597-603. [\[CrossRef\]](#)
13. Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of outcomes of COVID-19 in patients with chronic liver disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2021;19(7):1469-1479.e19. [\[CrossRef\]](#)
14. Chen L, Huang S, Yang J, Cheng X, Shang Z, Lu H, et al. Clinical characteristics in patients with SARS-CoV-2/HBV co-infection. *J Viral Hepat* 2020;27(12):1504-1507. [\[CrossRef\]](#)
15. Wu J, Yu J, Shi X, Li W, Song S, Zhao L, et al. Epidemiological and clinical characteristics of 70 cases of coronavirus disease and concomitant hepatitis B virus infection: A multicentre descriptive study. *J Viral Hepat* 2021;28(1):80-88. [\[CrossRef\]](#)
16. Chen X, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 and hepatitis b virus co-infection. *Virology* 2020;35(6):842-845. [\[CrossRef\]](#)
17. Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: A Multicenter Research Network Study. *Gastroenterology* 2020;159(2):768-771.e3. [\[CrossRef\]](#)
18. Zhang L, Hou J, Ma FZ, Li J, Xue S, Xu ZG. The common risk factors for progression and mortality in COVID-19 patients: a meta-analysis. *Arch Virol* 2021;166(8):2071-2087. [\[CrossRef\]](#)
19. Chien M, Anderson TK, Jockusch S, Tao C, Li X, Kumar S, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. *J Proteome Res* 2020;19(11):4690-4697. [\[CrossRef\]](#)
20. Lens S, Miquel M, Mateos-Muñoz B, García-Samaniego J, Forns X. SARS-CoV-2 in patients on antiviral HBV and HCV therapy in Spain. *J Hepatol* 2020;73(5):1262-1263. [\[CrossRef\]](#)