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Chronic Hepatitis B and COVID-19 Clinical Outcomes in the United States: A Multisite Retrospective Cohort Study

George A. Yendewa,[1,2] Temitope Olasehinde,[2] Frank Mulindwa,[3] Robert A. Salata,[1,2] Amir M. Mohareb,[4,5,6] and Jeffrey M. Jacobson[1,2]

[1]Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA, [2]Division of Infectious Diseases and HIV Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA, [3]Department of Medicine, United Health Services Wilson Medical Center, Johnson City, New York, USA, [4]Center for Global Health, Massachusetts General Hospital, Boston, Massachusetts, USA, [5]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA, and [6]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

Background. There is conflicting evidence regarding the impact of chronic hepatitis B virus (HBV) on SARS-CoV-2 outcomes. Additionally, the impact of SARS-CoV-2 vaccination and variant periods on outcomes in HBV/SARS-CoV-2 coinfection remain unexplored.

Methods. We utilized the TriNetX database to compare adults with HBV/SARS-CoV-2 (vs SARS-CoV-2 alone) across 97 US healthcare systems from 2020 to 2023. We assessed the odds of all inpatient hospitalizations, intensive care unit admissions, mechanical ventilation, 30-day, 90-day, and overall mortality. In sensitivity analyses, we excluded HIV, hepatitis C virus, and transplant cases and stratified the HBV/SARS-CoV-2 cohort by cirrhosis status. We applied propensity score matching to address confounding and reported odds ratios (OR) with 95% confidence intervals (CI).

Results. Of 4 206 774 individuals with SARS-CoV-2, about 0.2% (8293) were HBV/SARS-CoV-2. Individuals with HBV/SARS-CoV-2 (vs SARS-CoV-2 alone) had higher odds of intensive care unit admissions (OR, 1.18; 95% CI, 1.02–1.36), 90-day (OR, 1.22; 95% CI, 1.01–1.41) and overall mortality (OR, 1.18; 95% CI, 1.06–1.33). In sensitivity analyses, those with HBV/SARS-CoV-2 and cirrhosis had a 2.0- to 2.50-fold higher odds of adverse outcomes. Notably, even individuals with HBV/SARS-CoV-2 without cirrhosis had higher odds of mortality. Vaccinated (vs unvaccinated) individuals with HBV/SARS-CoV-2 had 57%, 54%, and 29% reduction in 30-day, 90-day, and overall mortality, respectively. The pre-Delta variant period was associated with higher odds of hospitalization compared to the Omicron but not the Delta period.

Conclusions. Chronic HBV was associated with worse SARS-CoV-2 outcomes, whereas SARS-CoV-2 vaccination reduced the likelihood of adverse outcomes.

Keywords. hepatitis b; mortality; SARS-CoV-2; vaccination; variants.

The convergence of 2 viral pandemics (ie, hepatitis B virus [HBV] and SARS-CoV-2), has presented complex clinical implications for dually infected individuals. HBV infects the liver and is a major global health concern, accounting for 296 million chronic cases and 820 000 million deaths in 2021, mostly from liver cirrhosis and hepatocellular carcinoma [1]. SARS-CoV-2, responsible for the ongoing COVID-19 pandemic, has led to >770 million cases and nearly 7 million attributable deaths [2]. SARS-CoV-2 primarily targets the lungs but also displays tropism toward the liver and multiple organ systems because of the ubiquitous expression of its obligate cellular receptor, angiotensin-converting enzyme 2 (ACE2) [3].

Emerging evidence suggests that individuals with preexisting chronic liver disease, especially cirrhosis, may face adverse outcomes after SARS-CoV-2 infection [4–7]. These initial studies have focused on chronic liver diseases from heterogeneous etiologies (eg, hepatic steatosis, alcoholic liver disease) [4–7]. However, recent research has specifically highlighted the risks for individuals with chronic HBV infection. In a 2022 systematic review and meta-analysis, Yu et al [8] reported a 2-fold higher odds of in-hospital mortality and a 1.90-fold higher odds of severe SARS-CoV-2 in individuals with chronic HBV infection. An updated meta-analysis in 2023 by Guo et al [9] confirmed these findings, observing a 1.65-fold higher odds of mortality and a 1.90-fold increased odds of severe SARS-CoV-2 in individuals with coexisting HBV infection. The pathophysiologic mechanisms associated with adverse SARS-CoV-2 outcomes in individuals with preexisting HBV

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Correspondence: George A. Yendewa, MD, Medicine (Infectious Diseases), Case Reserve Western University School of Medicine, Division of Infectious Diseases and HIV Medicine, University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH 44106 (gay7@case.edu). Alternate Corresponding Author. Jeffrey M. Jacobson, MD, Medicine, Case Reserve Western University School of Medicine, Division of Infectious Diseases and HIV Medicine, University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH 44106. E-mail: jxj573@case.edu.

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infection remain unclear. Proposed pathways include the direct cytopathic effects of SARS-CoV-2 on the liver [10], SARS-CoV-2–induced immune activation leading to the "cytokine storm" [11], drug-induced hepatic injury [12], and HBV reactivation [13]. The study by Guo et al [9] further suggested differences in SARS-CoV-2 outcomes based on geographic setting; however, their analysis included studies from only 3 countries, each of moderate HBV endemicity—China, South Korea, and Turkey, with 13 of 18 the studies conducted in China.

There may be HBV-specific pathways distinct from chronic liver diseases or cirrhosis that may contribute to adverse outcomes following SARS-CoV-2 infection; however, this remains unexplored. For instance, HBV can induce hepatocellular carcinoma through direct oncogenic pathways, independent of liver cirrhosis or decompensated liver disease [14]. Additionally, HBV infection is often complicated by co-infections such as HIV and hepatitis C virus (HCV) because of shared risk factors [15, 16]. These co-infections are known to significantly influence the natural history, disease progression, and clinical outcomes of HBV infection [15, 16], raising questions about how they might alter the dynamics between HBV and SARS-CoV-2. Other unresolved questions include the effectiveness of SARS-CoV-2 vaccination and the potential impact of SARS-CoV-2 variant type on clinical outcomes in individuals with pre-existing chronic HBV infection. To address these knowledge gaps, there is a need for comprehensive, large-scale studies from diverse regions to explore the nature of the interactions between HBV and SARS-CoV-2.

In this multicenter retrospective cohort study in the United States, our primary objective was to assess the clinical features and outcomes of SARS-CoV-2 infection among individuals with chronic HBV in a setting of low HBV endemicity. Our secondary objectives were to determine whether there are HBV-specific associations between chronic HBV infection and SARS-CoV-2 outcomes, excluding the impact of coinfections, immunocompromising conditions and advanced liver disease (ie, HIV, HCV, organ transplants, and cirrhosis). Additionally, we aimed to examine the associations between SARS-CoV-2 variants, SARS-CoV-2 vaccination, and clinical outcomes in individuals with concurrent SARS-CoV-2 and chronic HBV infection.

METHODS

Data Source

We conducted a multicenter retrospective cohort study of adults aged ≥18 years with preexisting chronic HBV using TriNetX, a global federated health research network. We sourced data from 97 healthcare organizations (HCOs) across the United States during the period from 1 January 2020 to 15 August 2023 (the last date of TriNetX access). The TriNetX research network provides access to continuously aggregated and deidentified electronic health record data, including diagnoses, procedures, medications, and laboratory values. To preserve patient privacy and confidentiality, TriNetX excludes geographical and institutional specifics of participating HCOs. However, a typical participating HCO generally comprises a prominent academic health center supplemented by main and satellite hospitals, specialized care services, and outpatient clinics.

Cohort Selection, Study Definitions, and Outcomes

We included all adults (≥18 years) in the TriNetX database with confirmed SARS-CoV-2, positive SARS-CoV-2–related RNA test, or positive Rapid Antigen test (International Classification of Diseases 10th Revision [ICD-10] codes: U07.1, U07.2, or J12.82). We identified individuals with SARS-CoV-2 with a diagnosis of chronic HBV (ICD-10: B18.0 or B18.1). We further stratified cases into 2 primary cohorts: those with chronic HBV (ie, HBV/SARS-CoV-2) and those without chronic HBV (ie, SARS-CoV-2 alone). For both cohorts, we collected data on patient demographics (age, sex, race, and ethnicity), comorbid conditions as defined by ICD-10 codes (ie, overweight/obesity, cardiovascular diseases, diabetes, chronic kidney diseases, chronic obstructive lung diseases, neoplasms, transplanted organs, HIV, HCV), nicotine dependence, alcohol-related disorders, SARS-CoV-2 vaccination status (receipt of at least 1 dose of vaccine), and SARS-CoV-2 treatment history (ie, dexamethasone, methylprednisolone, remdesivir, and nirmatrelvir-ritonavir).

Furthermore, we collected baseline laboratory parameters (within 30 days after index SARS-CoV-2 diagnosis). These included complete blood count (leukocytes, hemoglobin, platelet counts), renal function (creatinine, glomerular filtration rate), coagulation parameters (prothrombin time, international normalized ratio, activated partial thromboplastin time, D-dimer), hepatic function markers (alkaline phosphatase, aspartate transaminase, alanine aminotransferase, γ-glutamyl transferase), total and direct bilirubin, lipid profiles (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), lactate, troponin, B-type natriuretic peptide, lactate dehydrogenase, HBV DNA, HCV RNA, and HIV RNA levels.

Our primary outcomes of interest were the odds of all inpatient hospitalization intensive care unit (ICU) admission, mechanical ventilation, and all-cause early (30-day), late (90-day), and overall mortality, defined as mortality during the entire follow-up period and not restricted to 30 or 90 days following the index SARS-CoV-2 diagnosis. In the primary analysis, we compared these outcomes in all eligible cases of HBV/SARS-CoV-2 versus cases of SARS-CoV-2 without HBV.

To evaluate the differential impact of chronic HBV on SARS-CoV-2 outcomes, we performed 3 sensitivity analyses, specifically addressing potential confounding from HIV,

HCV, and organ transplants because these factors are known to influence the natural history and progression of HBV. The sensitivity analyses were as follows: (1) cases of HBV/SARS-CoV-2 compared with SARS-CoV-2 alone, but excluding HIV, HCV, and organ transplants from both cohorts; (2) cases of HBV/SARS-CoV-2 with cirrhosis compared with SARS-CoV-2 alone but excluding HIV, HCV, and organ transplants from both cohorts; and (3) cases of HBV/SARS-CoV-2 without cirrhosis compared with SARS-CoV-2 alone excluding HIV, HCV, and organ transplants from both cohorts.

In subgroup analyses of individuals with HBV/SARS-CoV-2, we further assessed the effect of SARS-CoV-2 vaccination (defined as receipt of 1 or more doses of any SARS-CoV-2 vaccine) and the impact of SARS-CoV-2 variants on outcomes. Because TriNetX does not provide information on SARS-CoV-2 variants, we used SARS-CoV-2 variant dominance periods for the United States, as reported by the United States Center for Disease Control and Prevention (CDC) [23]: (1) 1 January 2020 to 30 June 2021 for pre-Delta (ie, Alpha, Beta, Gamma) variant dominance; (2) 1 July 2021 to 30 November 2021 for Delta variant dominance; and (3) 1 December 2021 to 15 August 2023 for Omicron variant dominance. We have provided details of the ICD-10 and other codes used for querying the TriNetX database in the Supplementary File.

Statistical Analyses

We performed all statistical analyses in the online TriNetX Advanced Analytics platform. We reported continuous variables with mean ± standard deviation and categorical variables as frequencies and percentages. We addressed potential confounding using 1:1 greedy nearest-neighbor propensity score matching of cohorts by the following variables: age at SARS-CoV-2 diagnosis, sex, race, ethnicity, comorbidities (ie, overweight/obesity, diseases of liver, ischemic heart diseases, hypertensive diseases, heart failure, heart failure, diabetes, chronic lung diseases, chronic kidney diseases, neoplasms, organ transplants, HIV, and HCV), nicotine dependence, alcohol-related disorders, SARS-CoV-2 vaccination, and SARS-CoV-2 treatments (ie, dexamethasone, methylprednisolone, remdesivir, nirmatrelvir-ritonavir). We compared continuous variables using independent *t*-tests and categorical variables with chi-square tests. For outcomes of interest, we reported odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), with statistical significance set at $P < .05$.

Participant Consent Statement

We obtained ethical approval from the institutional review board at Case Western Reserve University/University Hospitals Cleveland Medical Center, which granted a waiver. Additionally, TriNetX obtained a waiver from WCG IRB Connexus. Written informed consent was not necessary, as the TriNetX system protects patient information by only providing deidentified and aggregated data.

RESULTS

Baseline Characteristics

Of the 4 206 774 individuals with confirmed SARS-CoV-2 in the primary analysis, about 0.2% (8293) had preexisting chronic HBV (ie, HBV/SARS-CoV-2) (Table 1). Compared with those with SARS-CoV-2 only, individuals with HBV/SARS-CoV-2 were significantly more likely to be older, male, White, and have a higher burden of liver cirrhosis (18.0% vs 0.8%), chronic liver diseases (46.5% vs 6.2%), ischemic heart diseases (21.1% vs 9.0%), hypertensive diseases (52.9% vs 27.8%), heart failure (12.5% vs 4.8%), cerebrovascular diseases (12.8% vs 5.3%), diabetes (30.5% vs 12.6%), chronic lower respiratory diseases (26.8% vs 17.1%), chronic kidney diseases (23.3% vs 6.2%), smoking (15.7% vs 8.6%), alcohol-related disorders (8.4% vs 2.7%), and neoplasms (51.1% vs 21.1%). Furthermore, individuals with HBV/SARS-CoV-2 (vs SARS-CoV-2 alone) were more likely to have a history of HIV (6.8% vs 0.4%), HCV (13.6% vs 0.6%), and transplanted organs (10.1% vs 1.0%). Additionally, individuals with HBV/SARS-CoV-2 (vs SARS-CoV-2 alone) were more likely to receive COVID-19 treatments like dexamethasone (35.6% vs 18.5%), methylprednisolone (27.6% vs 17.5%), remdesivir (2.1% vs 0.1%), and nirmatrelvir-ritonavir (1.8% vs 0.6%). Disparities between cohorts were mostly eliminated with propensity score matching; however, the burden of liver cirrhosis (18.0% vs 13.8%) and HCV (13.6% vs 11.7%) remained higher in the HBV/SARS-CoV-2 cohort compared with SARS-CoV-2 alone (all $P < .001$).

Baseline Laboratory Parameters

A subset of participants had baseline laboratory parameters measured within one month after the index SARS-CoV-2 diagnosis. Among these, individuals with HBV/SARS-CoV-2 coinfection were more likely to exhibit evidence of end-organ damage at baseline compared to those in the SARS-CoV-2–only cohort (Table 2). This included lower hemoglobin, reduced platelet counts, elevated serum creatinine, and reduced estimated glomerular filtration rate. Additionally, markers of hepatic injury were higher in the HBV/SARS-CoV-2 group compared with the SARS-CoV-2-only group including aspartate transaminase (35 IU/L vs 25 IU/L), alanine aminotransferase (34 IU/L vs 26 IU/L), γ-glutamyl transferase (97 IU/L vs 74 IU/L), along with lower serum albumin and total and direct bilirubin (all $P < .01$). Moreover, individuals with HBV/SARS-CoV-2 had higher levels of acute-phase reactants including CRP, ESR, ferritin, and procalcitonin compared with those with SARS-CoV-2 alone (all $P < .001$). Propensity score matching partially balanced the cohorts;

Table 1. Comparison of Baseline Characteristics Before and After Propensity Score Matching

	Before Matching			After Matching		
Variables	HBV/SARS-CoV-2	SARS-CoV-2	*P*-Value	HBV/SARS-CoV-2	SARS-CoV-2	*P*-Value
Total	*n* = 8293	*n* = 4 198 481		*n* = 8293	*n* = 8293	
Age at index (years)[a]	56.5 ± 14.2	48.4 ± 19.4	<.001	56.5 ± 14.1	56.6 ± 15.1	.643
Gender						
Male	4580 (55.2%)	1 734 284 (41.3%)	<.001	4580 (55.2%)	4590 (55.3%)	.815
Female	3648 (44.0%)	2 351 777 (56.0%)	<.001	3670 (44.0%)	3687 (44.2%)	.791
Body mass index (kg/m^2)[a]	27.0 ± 6.3	29.9 ± 7.6	<.001	27.0 ± 6.3	29.3 ± 7.1	<.001
Race or ethnicity						
White	1852 (22.3%)	2 507 530 (59.7%)	<.001	1852 (22.3%)	1807 (21.8%)	.399
Asian	2706 (32.6%)	156 415 (3.7%)	<.001	2706 (32.6%)	2765 (33.3%)	.330
Unknown race	1722 (20.6%)	631 256 (15.3%)	<.001	1722 (20.7%)	1737 (20.8%)	.774
Black or African American	1542 (18.6%)	597 960 (14.2%)	<.001	1542 (18.6%)	1513 (18.2%)	.561
Hispanic or Latino	189 (2.3%)	26 302 (0.6%)	<.001	381 (4.6%)	335 (4.0%)	.079
Native Hawaiian or other Pacific islander	381 (4.6%)	442 601 (10.5%)	<.001	189 (2.3%)	175 (2.1%)	.458
Other race	331 (4.0%)	264 447 (4.0%)	<.001	330 (4.5%)	378 (4.0%)	.065
Comorbidities						
Liver cirrhosis	1492 (18.0%)	33 624 (0.8%)	<.001	1492 (18.0%)	1143 (13.8%)	<.001
Diseases of liver	3855 (46.5%)	261 197 (6.2%)	<.001	3855 (46.5%)	3950 (47.6%)	.139
Ischemic heart diseases	1750 (21.1%)	378 104 (9.0%)	<.001	1750 (21.1%)	1735 (20.9%)	.775
Hypertensive diseases	4391 (52.9%)	1 166 289 (27.8%)	<.001	4391 (52.9%)	4415 (53.2%)	.709
Heart failure	1037 (12.5%)	202 151 (4.8%)	<.001	1037 (12.5%)	1025 (12.4%)	.778
Diabetes mellitus	2530 (30.5%)	529 165 (12.6%)	<.001	2530 (30.5%)	2526 (30.5%)	.946
Overweight or obesity	1626 (19.5%)	708 223 (17.1%)	<.001	1624 (19.5%)	1922 (23.1%)	<.001
Chronic lower respiratory diseases	2226 (26.8%)	717 382 (17.1%)	<.001	2226 (26.8%)	2233 (26.9%)	.902
Chronic kidney disease	1936 (23.3%)	261 866 (6.2%)	<.001	1936 (23.3%)	1882 (22.7%)	.319
Cerebrovascular diseases	1059 (12.8%)	224 545 (5.3%)	<.001	1059 (12.8%)	1042 (12.6%)	.691
Transplanted organ and tissue	846 (10.1%)	41 966 (1.0%)	<.001	845 (10.1%)	808 (9.7%)	.338
Neoplasms	4259 (51.0%)	870 998 (21.1%)	<.001	4249 (51.0%)	4352 (52.2%)	.110
HIV disease	567 (6.8%)	15 953 (0.4%)	<.001	563 (6.8%)	514 (6.2%)	.123
Chronic HCV	1130 (13.6%)	26 359 (0.6%)	<.001	1130 (13.6%)	973 (11.7%)	<.001
Lifestyle risk factors						
Nicotine-related disorders	1306 (15.7%)	361 641 (8.6%)	<.001	1306 (15.7%)	1225 (14.8%)	.080
Alcohol-related disorders	700 (8.4%)	114 258 (2.7%)	<.001	700 (8.4%)	639 (7.7%)	.082
SARS-CoV-2 vaccine	1778 (21.4%)	453 467 (10.8%)	<.001	1696 (20.3%)	1624 (19.5%)	.163
SARS-CoV-2 treatments						
Dexamethasone	2949 (35.6%)	775 329 (18.5%)	<.001	2949 (35.6%)	2924 (35.3%)	.685
Methylprednisolone	2290 (27.6%)	735 001 (17.5%)	<.001	2290 (27.6%)	2235 (27.0%)	.338
Remdesivir	173 (2.1%)	6030 (0.1%)	<.001	138 (2.0%)	117 (1.7%)	.184
Nirmatrelvir/ritonavir	149 (1.8%)	24 529 (0.6%)	<.001	137 (2.0%)	138 (2.0%)	.951
HBV treatments						
Entecavir	1667 (20.1%)	–	–	1667 (20.1%)	–	–
Tenofovir alafenamide	1280 (15.4%)	–	–	1280 (15.4%)	–	–
Tenofovir disoproxil	1280 (15.4%)	–	–	1280 (15.4%)	–	–
Emtricitabine	617 (7.4%)	–	–	617 (7.4%)	–	–
Lamivudine	368 (4.4%)	–	–	368 (4.4%)	–	–

HBV/SARS-CoV-2, individuals with HBV and SARS-CoV-2; SARS-CoV-2 only, individuals with SARS-CoV-2 without HBV.

[a]Mean ± standard deviation.

however, higher levels of markers of liver disease and inflammation persisted in the HBV/SARS-CoV-2 group compared with their SARS-CoV-2–only counterparts. There was no differences between groups in HBV DNA, HIV RNA, and HCV RNA levels.

Clinical Outcomes of SARS-CoV-2 in Primary Analyses

Inpatient hospital admission rates were similar between the cohorts (11.2% vs 11.6%); however, individuals with HBV/SARS-CoV-2 experienced higher rates of ICU admission (5.9% vs 3.0%), mechanical ventilation (2.3% vs 0.9%), 30-day mortality (2.2% vs 1.3%), 90-day mortality (3.3% vs 1.8%), and overall mortality (8.7% vs 4.0%) (all $P < .001$)

Table 2. Comparison of Baseline Laboratory Parameters Before and After Propensity Score Matching

	Before Matching			After Matching		
Variables	HBV/SARS-CoV-2	SARS-CoV-2	*P* Value	HBV/SARS-CoV-2	SARS-CoV-2	*P* Value
Leukocytes ($\times 10^9$/L)[a]	9.2 ± 98.9	11.7 ± 129.8	<.001	9.2 ± 99.2	11.9 ± 141.7	<.001
n (%)	6462 (87.6%)	2 159 576 (55.0%)		6319 (77.9%)	5930 (71.1%)	
Hemoglobin (g/dL)[a]	12.8 ± 2.3	13.3 ± 1.9	<.001	12.7 ± 2.3	12.9 ± 2.2	<.001
n (%)	7135 (82.4%)	2 305 308 (54.9%)		7135 (86.0%)	6565 (76.1%)	
Platelets ($\times 10^9$/L) [a]	216 ± 90	254 ± 78	<.001	215 ± 90	241 ± 86	<.001
n (%)	6833 (77.9%)	2 305 308 (54.9%)		6833 (82.4%)	6360 (76.7%)	
Creatinine (mg/dL) [a]	1.5 ± 5.9	1.0 ± 2.9	<.001	1.6 ± 5.9	1.5 ± 5.7	.831
n (%)	7261 (87.6%)	2 307 963 (55.0%)		7259 (87.1%)	6690 (80.3%)	
GFR (mL/min/1.73 m^2), n (%)	79 ± 33	83 ± 29	<.001	78 ± 33	76 ± 31	.115
	7255 (87.5%)	2 186 766 (52.1%)		7251 (87.1%)	6649 (79.8%)	
Hemoglobin A1c (%)[a]	6.1 ± 1.4	6.1 ± 1.6	.579	6.1 ± 1.4	6.2 ± 1.5	.133
	4905 (59.2%)	242 631 (29.6%)		4905 (59.0%)	4530 (54.3%)	
Prothrombin time (seconds)[a,] n (%)	12.7 ± 3.3	13.1 ± 4.6	<.001	12.7 ± 3.3	12.8 ± 3.4	.115
	4969 (59.9%)	781 328 (18.6%)		4950 (59.3%)	4012 (48.1%)	
INR[a]	1.1 ± 0.8	1.1 ± 0.5	.003	1.1 ± 0.8	1.1 ± 1.1	.207
n (%)	5207 (62.8%)	858 451 (20.4%)		5198 (62.4%)	4143 (49.7%)	
ATTP (seconds)[a]	31 ± 10	31 ± 11	.364	30.9 ± 9.8	30.5 ± 9.0	.827
n (%)	4002 (49.3%)	682 288 (16.3%)		3906 (48.1%)	3426 (41.1%)	
Alkaline phosphatase (IU/L)[a]	97 ± 85	82 ± 48	<.001	98 ± 85	93 ± 78	.010
n (%)	6651 (80.2%)	2 062 264 (49.1%)		6651 (79.8%)	6112 (73.3%)	
AST (IU/L)[a]	35 ± 74	25 ± 42	<.001	35 ± 75	31 ± 52	<.001
n (%)	7266 (87.6%)	2 115 937 (50.4%)		7244 (87.2%)	6485 (77.8%)	
ALT (IU/L)[a]	34 ± 86	26 ± 37	<.001	34 ± 87	30 ± 58	<.001
n (%)	7330 (88.4%)	2 134 845 (50.8%)		7327 (87.9%)	6555 (78.6%)	
GGT (IU/L)[a]	97 ± 226	74 ± 165	<.001	100 ± 230	110 ± 247	.684
n (%)	1808 (21.8%)	145 067 (3.5%)		1802 (22.2%)	1399 (16.8%)	
Total bilirubin (mg/dL)[a]	0.7 ± 1.2	0.6 ± 0.6	<.001	0.7 ± 1.2	0.7 ± 1.2	.124
n (%)	6985 (84.2%)	2 032 560 (48.4%)		6974 (83.9%)	6253 (75.0%)	
Direct bilirubin (mg/dL)[a]	0.4 ± 1.4	0.3 ± 1.0	<.001	0.4 ± 1.3	0.4 ± 1.4	.976
n (%)	4197 (50.6%)	623 544 (14.9%)		4189 (51.5%)	3384 (40.6%)	
Total protein (mg/dL)[a]	7.1 ± 0.9	7.1 ± 0.8	.165	7.1 ± 0.9	7.1 ± 0.8	.736
n (%)	5929 (71.5%)	1 932 320 (46.0%)		5922 (71.3%)	5550 (66.6%)	
Albumin (g/dL)[a]	4.0 ± 0.6	4.1 ± 0.5	<.001	4.0 ± 0.6	4.0 ± 0.6	.998
n (%)	6724 (81.1%)	2 034 262 (48.5%)		6724 (80.7%)	6121 (73.4%)	
Total cholesterol (mg/dL)[a], n (%)	169 ± 45	178 ± 44	<.001	168 ± 45	171 ± 45	.008
	5309 (64.0%)	1 591 224 (37.9%)		5301 (63.8%)	5113 (61.3%)	
HDL (mg/dL)[a]	50 ± 17	51 ± 18	<.001	50 ± 18	50 ± 18	.010
n (%)	5064 (61.1%)	1 605 848 (38.2%)		5033 (60.9%)	4974 (59.7%)	
LDL (mg/dL)[a]	94 ± 36	102 ± 36	<.001	94 ± 36	95 ± 36	<.001
n (%)	5082 (61.3%)	1 590 109 (37.9%)		5080 (61.2%)	4984 (59.8%)	
Triglycerides (mg/dL)[a]	128 ± 114	130 ± 102	0.490	129 ± 115	135 ± 101	.163
n (%)	4700 (56.7%)	1 597 570 (38.1%)		4678 (56.8%)	4578 (54.9%)	
Lactate dehydrogenase	280 ± 261	264 ± 302	<.001	272 ± 332	274 ± 374	.266
(mg/dL)[a], n (%)	2419 (29.2%)	235 291 (5.6%)		2544 (30.5%)	1905 (22.9%)	
Troponin (mg/dL)[a]	0.5 ± 3.6	0.6 ± 9.9	.680	0.4 ± 3.5	0.6 ± 11.1	.607
n (%)	1044 (12.2%)	244 623 (6.0%)		961 (12.5%)	980 (12.3%)	
Natriuretic peptide B (pg/mL)[a], n (%)	406 ± 1055	416 ± 2314	.893	434 ± 1643	432 ± 2282	.654
	1093 (13.1%)	214 785 (5.3%)		954 (11.3%)	928 (11.1%)	
Ferritin (ng/dL)[a]	459 ± 931	214 ± 772	<.001	474 ± 938	419 ± 927	<.001
n (%)	2958 (35.5%)	516 269 (12.3%)		2900 (35.0%)	2433 (29.2%)	
Procalcitonin (ng/mL)[a]	2.5 ± 8.9	1.8 ± 7.2	.011	2.4 ± 9.0	2.7 ± 10.1	.667
n (%)	686 (9.8%)	74 708 (2.3%)		686 (9.8%)	475 (6.8%)	
Fibrin D-dimer (ng/mL)[a]	433 ± 1388	336 ± 4077	0.534	433 ± 1373	325 ± 978	.248
n (%)	674 (9.6%)	139 264 (4.3%)		674 (9.6%)	577 (8.2%)	
C-reactive protein (mg/dL)[a], n (%)	23.9 ± 48.7	21.7 ± 45.5	.011	24 ± 49	21 ± 44	.022
	2913 (35.1%)	502 612 (12.0%)		2849 (35.0%)	2382 (28.6%)	
Erythrocyte sedimentation rate (mm/hour)[a], n (%)	33 ± 32	22 ± 23	<.001	33 ± 32	29 ± 29	<.001
	1874 (22.6%)	550 844 (13.1%)		1862 (22.3%)	1715 (20.6%)	
Lactate (mg/mL)[a],	1.5 ± 0.8	1.4 ± 1.0	.038	1.5 ± 0.8	1.4 ± 1.2	.773
n (%)	1932 (23.2%)	367 048 (8.9%)		1451 (20.9%)	1475 (21.3%)	

Table 2. Continued

Variables	Before Matching			After Matching		
	HBV/SARS-CoV-2	SARS-CoV-2	*P* Value	HBV/SARS-CoV-2	SARS-CoV-2	*P* Value
						-
HBV DNA (log IU/mL)[a] n (%)	5.2 ± 0.4 1365 (16.4%)	-	-	5.2 ± 0.4 1365 (16.4%)	-	-
HCV RNA (log IU/mL) [a] n (%)	6.1 ± 0.4 210 (18.6%)[b]	6.1 ± 0.5 10 693 (40.6%) [b]	.972	6.1 ± 0.4 210 (18.6%) [b]	6.0 ± 0.5 180 (18.5%) [b]	.445
HIV RNA (log copies/mL) [a] n (%)	2.1 ± 1.3 172 (30.3%) [b]	2.1 ± 1.5 5081 (31.8%) [b]	.887	2.0 ± 1.1 172 (30.6%) [b]	1.9 ± 1.5 150 (29.2%) [b]	.458

N (%), Number and percentage of individuals with available laboratory values out of the total population in the group.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ATTP, activated partial thromboplastin time; GGT, gamma-glutamyl transferase; HBV/SARS-CoV-2, individuals with HBV and SARS-CoV-2; INR, international normalized ratio; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SARS-CoV-2, individuals with SARS-CoV-2 without HBV.

[a]Mean ± standard deviation.

[b]Indicates proportion of subgroup of participants with available baseline data for the corresponding parameter.

Table 3. Clinical Outcomes in Primary Analysis

Outcomes	Before Matching				After Matching			
	HBV/SARS-CoV-2	SARS-CoV-2	OR (95% CI)	*P* value	HBV/SARS-CoV-2	SARS-CoV-2	OR (95% CI)	*P* value
Hospitalization	364 (11.2%)	334 346 (11.6%)	0.96 (0.86–1.08)	.508	364 (11.2%)	461 (12.0%)	0.93 (0.80–1.08)	.327
Intensive care unit	425 (5.9%)	119 616 (3.0%)	2.01 (1.83–2.22)	<.001	423 (5.9%)	373 (5.1%)	1.18 (1.02–1.36)	.024
Mechanical ventilation	183 (2.3%)	34 817 (0.9%)	2.73 (2.36–3.16)	<.001	182 (2.3%)	140 (1.7%)	1.31 (1.05–1.64)	.016
Mortality (30-day)	178 (2.2%)	55 954 (1.3%)	1.63 (1.41–1.89)	<.001	178 (2.2%)	153 (1.9%)	1.17 (0.94–1.46)	.158
Mortality (90-day)	274 (3.3%)	75 795 (1.8%)	1.87 (1.65–2.11)	<.001	274 (3.3%)	224 (2.7%)	1.22 (1.01–1.41)	.042
Mortality (overall)	722 (8.7%)	163 160 (4.0%)	2.32 (2.14–2.50)	<.001	721 (8.7%)	617 (7.5%)	1.18 (1.06–1.33)	.003

Abbreviations: CI, confidence interval; HBV/SARS-CoV-2, individuals with HBV and SARS-CoV-2; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, individuals with SARS-CoV-2 without HBV.

compared with those with SARS-CoV-2 alone (Table 3). After propensity score matching, individuals with HBV/SARS-CoV-2 had significantly higher odds of ICU admissions (OR, 1.18; 95% CI, 1.02–1.36; $P = .024$), 90-day mortality (OR, 1.22; 95% CI, 1.01–1.41; $P = .042$), and overall mortality (OR, 1.18; 95% CI, 1.06–1.33; $P = .003$) compare with those with SARS-CoV-2 alone.

Clinical Outcomes of SARS-CoV-2 in Sensitivity Analyses

After excluding cases of HIV, HCV, and organ transplants, individuals with HBV/SARS-CoV-2 (vs SARS-CoV-2 alone) still experienced higher odds of ICU admissions (OR, 1.33; 95% CI, 1.09–1.61; $P = .004$), mechanical ventilation (OR, 1.40; 95% CI, 1.03–1.91; $P = .033$), 90-day mortality (OR, 1.26; 95% CI, 1.01–1.59; $P = .044$), and overall mortality (OR, 1.31; 95% CI, 1.13–1.53; $P < .001$) (Table 4). The highest odds of adverse outcomes were observed in the subgroup of individuals with cirrhosis and HBV/SARS-CoV-2 (vs cirrhosis and SARS-CoV-2 alone), as follows: ICU admissions (OR, 2.50; 95% CI, 1.49–4.19; $P < .001$), mechanical ventilation (OR, 2.29; 95% CI, 1.08–4.87; $P = .027$), 30-day mortality (OR, 2.04; 95% CI, 1.11–3.76; $P = .019$), 90-day mortality (OR, 2.12; 95% CI, 1.28–3.49; $P = .003$), and overall mortality (OR, 2.21; 95% CI, 1.57–3.12; $P < .001$). Even among individuals with HBV/SARS-CoV-2 without cirrhosis, there were higher odds of mechanical ventilation (OR, 1.78; 95% CI, 1.21–2.62; $P = .003$) and overall mortality (OR, 1.18; 95% CI, 1.01–1.41; $P = .048$) compared with the SARS-CoV-2-only group.

Impact of SARS-Cov-2 Vaccination on Clinical Outcomes

At baseline, the SARS-CoV-2 vaccination rates were higher among individuals with HBVSARS-CoV-2 than in their SARS-CoV-2-only counterparts (21.4% vs 10.8%, $P < .001$) (Table 1). In subgroup analysis of the primary HBV/SARS-CoV-2 cohort, there were similar rates of hospitalization (12.2% vs 10.1%), mechanical ventilation (2.7% vs 2.4%), and ICU admissions (7.2% vs 7.0%) (Table 5); however, those in the HBV/SARS-CoV-2 group had lower rates of 30-day mortality (1.2% vs 2.8%), 90-day mortality (2.1% vs 4.6%) and overall mortality (7.9% vs 10.9%). After propensity score matching, vaccinated individuals with HBV/SARS-CoV-2 remained at lower odds of 30-day mortality (OR, 0.43; 95% CI, .27–.69; $P < .001$), 90-day mortality (OR, 0.46; 95% CI, .32–.65; $P < .001$), and overall mortality (OR, 0.71; 95% CI, .58–.87; $P = .001$).

Table 4. Sensitivity Analyses of Clinical Outcomes in Subgroups Excluding HIV, HCV, Organ Transplants, or Cirrhosis

	Before Matching				After Matching			
Outcomes	HBV/SARS-CoV-2	SARS-CoV-2	OR (95% CI)	*P* Value	HBV/SARS-CoV-2	SARS-CoV-2	OR (95% CI)	*P* Value
Subgroup of All Cases (Excluding HIV, HCV, and Organ Transplants)								
Hospitalization	287 (10.2%)	325 135 (11.4%)	0.88 (0.78–1.00)	.048	287 (10.2%)	396 (11.4%)	0.89 (0.76–1.04)	.141
Intensive care unit	240 (4.2%)	107 405 (2.8%)	1.52 (1.34–1.74)	<.001	240 (4.2%)	187 (3.2%)	1.33 (1.09–1.61)	.004
Mechanical ventilation	99 (1.6%)	29 726 (0.7%)	2.16 (1.77–2.64)	<.001	96 (1.6%)	69 (1.1%)	1.40 (1.03–1.91)	.033
Mortality (30-day)	101 (1.6%)	49 020 (1.2%)	1.31 (1.07–1.59)	.008	100 (1.6%)	85 (1.4%)	1.18 (0.88–1.58)	.267
Mortality (90-day)	175 (2.8%)	66 811 (1.7%)	1.67 (1.44–1.94)	<.001	172 (2.8%)	137 (2.2%)	1.26 (1.01–1.59)	.044
Mortality (overall)	418 (6.7%)	142 479 (3.6%)	1.91 (1.73–2.11)	<.001	415 (6.7%)	321 (5.2%)	1.31 (1.13–1.53)	<.001
Subgroup of Cases With Cirrhosis (Excluding HIV, HCV, Organ Transplants)								
Hospitalization	28 (13.7%)	330 904 (11.9%)	1.17 (0.79–1.75)	.434	25 (13.2%)	30 (9.9%)	1.39 (0.79–2.44)	.255
Intensive care unit	51 (8.6%)	114 744 (3.0%)	3.04 (2.28–4.05)	<.001	49 (8.9%)	22 (3.8%)	2.50 (1.49–4.19)	<.001
Mechanical ventilation	23 (3.3%)	31 224 (0.8%)	4.29 (2.82–6.51)	<.001	22 (3.4%)	10 (1.5%)	2.29 (1.08–4.87)	.027
Mortality (30-day)	33 (4.5%)	52 969 (1.3%)	3.51 (2.47–4.98)	<.001	32 (4.7%)	16 (2.3%)	2.04 (1.11–3.76)	.019
Mortality (90-day)	52 (7.1%)	72 123 (1.8%)	4.15 (3.13–5.51)	<.001	49 (7.2%)	24 (3.5%)	2.12 (1.28–3.49)	.003
Mortality (overall)	119 (16.3%)	152 612 (3.8%)	4.88 (4.01–5.94)	<.001	110 (16.3%)	55 (8.1%)	2.21 (1.57–3.12)	<.001
Subgroup of Cases Without Cirrhosis (Excluding HIV, HCV, Organ Transplants)								
Hospitalization	243 (9.0%)	299 943 (10.6%)	0.83 (0.72–0.95)	.006	243 (9.0%)	330 (10.4%)	0.85 (0.72–1.01)	.071
Intensive care unit	171 (3.3%)	102 096 (2.7%)	1.25 (1.07–1.45)	.005	171 (3.4%)	168 (3.3%)	1.02 (0.82–1.27)	.837
Mechanical ventilation	73 (1.3%)	27 608 (0.7%)	1.86 (1.47–2.35)	<.001	72 (1.3%)	41 (0.8%)	1.78 (1.21–2.62)	.003
Mortality (30-day)	74 (1.3%)	51 653 (1.3%)	1.05 (0.84–1.32)	.661	74 (1.3%)	71 (1.3%)	1.04 (0.75–1.45)	.799
Mortality (90-day)	131 (2.4%)	66 811 (1.7%)	1.41 (1.18–1.68)	<.001	131 (2.4%)	145 (2.6%)	0.90 (0.71–1.14)	.388
Mortality (overall)	314 (5.6%)	142 479 (3.6%)	1.55 (1.38–1.74)	<.001	304 (5.6%)	264 (4.8%)	1.18 (1.01–1.41)	.048

Abbreviations: CI, confidence interval; HBV/SARS-CoV-2, individuals with HBV and SARS-CoV-2; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, individuals with SARS-CoV-2 without HBV.

Table 5. Clinical Outcomes of HBV/SARS-CoV-2 by SARS-CoV-2 Vaccination Status

	Before Matching				After Matching			
Outcomes	HBV/SARS-CoV-2 + Vaccinated	HBV/ SARS-CoV-2+ Not Vaccinated	OR (95% CI)	*P* Value	HBV/ SARS-CoV-2+ Vaccinated	HBV/ SARS-CoV-2+ Not Vaccinated	OR (95% CI)	*P* Value
Hospitalization	46 (10·8%)	231 (9·3%)	1·18 (.84–1·65)	.339	46 (10·8%)	41 (7·9%)	1·40 (.90–2·18)	.133
Mechanical ventilation	27 (1·9%)	87 (1·4%)	1·35 (.88–2·09)	.171	27 (2·0%)	19 (1·4%)	1·42 (.79–2·56)	.245
Intensive care unit	75 (6·6%)	246 (4·6%)	1·48 (1·13–1·93)	.004	74 (6·5%)	57 (4·7%)	1·40 (.92–2·01)	.089
Mortality (30-day)	19 (1·3%)	174 (2·8%)	0·46 (.29-.75)	.001	18 (1·3%)	46 (3·3%)	0·38 (.22-.66)	<.001
Mortality (90-day)	35 (2·4%)	258 (4·2%)	0·58 (.40-.82)	.002	34 (2·4%)	71 (5·0%)	0·46 (.31-.70)	<.001
Mortality (overall)	76 (5·3%)	468 (7·6%)	0·68 (.53-.88)	.003	74 (5·2%)	125 (8·9%)	0·56 (.42-.76)	<.001

Abbreviations: CI, confidence interval; HBV/SARS-CoV-2; individuals with HBV and SARS-CoV-2; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, individuals with SARS-CoV-2 without HBV.

Impact of SARS-CoV-2 Variant Periods on Clinical Outcomes

Individuals with HBV/SARS-CoV-2 had higher odds of hospitalizations (OR, 1.41; 95% CI, 1.02–2.24; $P = .036$) during the pre-Delta versus Omicron variant waves (Table 6). Otherwise, there were no significant differences in outcomes differences in outcomes between the pre-Delta-Delta and Delta-Omicron dominance periods after matching.

DISCUSSIONS

This multicenter study in the United States represents 1 of the largest investigations to comprehensively characterize SARS-CoV-2 outcomes in individuals with underlying chronic HBV infection specifically, compared to previous studies that have focused on chronic liver disease of multiple etiologies [4–7]. Our findings revealed that individuals with chronic HBV experienced higher odds of adverse SARS-CoV-2 outcomes, including ICU admissions, mechanical ventilation, and death. The results corroborate previous studies in regions with higher HBV endemicity [8, 9]. In the United States, approximately 1.6 million individuals live with chronic HBV infection, amounting to about 0.65% of the adult population [17]. Recent years have witnessed an increase in HBV transmission in the United States, especially among individuals who use

Table 6. Clinical Outcomes by SARS-CoV-2 Variant Period

	Before Matching				After Matching			
Outcomes	HBV/SARS-CoV-2	SARS-CoV-2	OR (95% CI)	*P* Value	HBV/SARS-CoV-2	SARS-CoV-2	OR (95% CI)	*P* Value
Pre-Delta versus Delta Variant Periods (1 January 2020–30 June 2021)								
Hospitalization	205 (10.2%)	102 (8.8%)	1.17 (.91–1.50)	.224	96 (8.6%)	86 (8.1%)	1.08 (.80–1.46)	.624
Intensive care unit	210 (5.2%)	80 (3.2%)	1.62 (1.25–2.11)	<.001	94 (4.1%)	77 (3.3%)	1.23 (.91–1.68)	.180
Mechanical ventilation	94 (2.1%)	42 (1.6%)	1.33 (.92–1.93)	.124	44 (1.8%)	40 (1.6%)	1.10 (.72–1.70)	.660
Mortality (30-day)	95 (2.0%)	41 (1.5%)	1.38 (.95–1.99)	.088	49 (1.8%)	41 (1.5%)	1.20 (.79–1.82)	.392
Mortality (90-day)	149 (3.2%)	76 (2.7%)	1.16 (.88–1.54)	.289	81 (2.9%)	76 (2.7%)	1.07 (.78–1.47)	.684
Mortality (overall)	376 (8.0%)	179 (6.5%)	1.26 (1.05–1.52)	.013	174 (6.7%)	167 (6.5%)	1.05 (.84–1.31)	.670
Pre-Delta versus Omicron Variant Periods (1 July 2021–Nov 30, 2021)								
Hospitalization	193 (2.0%)	117 (1.2%)	1.48 (1.04–2.47)	.003	143 (2.0%)	101 (1.3%)	1.41 (1.02–2.24)	.036
Intensive care unit	206 (5.2%)	127 (3.7%)	1.45 (1.15–1.18)	.001	140 (4.5%)	120 (3.8%)	1.17 (.91–1.50)	.210
Mechanical ventilation	94 (2.2%)	50 (1.3%)	1.64 (1.16–2.31)	.005	65 (1.9%)	46 (1.3%)	1.42 (.97–2.2.08)	.070
Mortality (30-day)	105 (2.1%)	77 (1.9%)	1.15 (.85–1.54)	.371	69 (1.9%)	69 (1.9%)	1.00 (.72–1.40)	.995
Mortality (90-day)	147 (3.2%)	130 (3.3%)	0.97 (.76–1.23)	.788	109 (3.1%)	113 (3.2%)	0.97 (.74–1.26)	.798
Mortality (overall)	368 (8.1%)	285 (7.3%)	1.12 (.95–1.31)	.183	266 (7.5%)	260 (73%)	1.03 (.86–1.23)	.765
Delta versus Omicron Variant Periods (1 December 2021–15 August 2023)								
Hospitalization	94 (8.2%)	118 (8.0%)	1.03 (.77–1.36)	.864	92 (8.0%)	76 (7.2%)	1.14 (.83–1.56)	.430
Intensive care unit	82 (3.3%)	134 (3.8%)	0.88 (.66–1.16)	.352	81 (3.3%)	85 (3.5%)	0.95 (.70–1.30)	.756
Mechanical ventilation	43 (1.6%)	54(1.4%)	1.16 (.77–1.73)	.484	43 (1.6%)	34 (1.3%)	1.27 (.81–1.99)	.306
Mortality (30-day)	44 (1.6%)	77 (1.9%)	0.82 (.57–1.19)	.303	44 (1.6%)	43 (1.6%)	1.02 (.67–1.56)	.921
Mortality (90-day)	81 (2.9%)	136 (3.4%)	0.86 (.65–1.13)	.274	81 (2.9%)	76 (2.7%)	1.07 (.78–1.46)	.694
Mortality (overall)	185 (6.6%)	297 (7.4%)	0.89 (.74–1.08)	.239	185 (6.7%)	185 (6.7%)	1.00 (.80–1.23)	.986

Abbreviations: CI, confidence interval; HBV/SARS-CoV-2, individuals with HBV and SARS-CoV-2; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, individuals with SARS-CoV-2 without HBV.

drugs and those at risk of sexual transmission [18]. Considering the escalating public health challenge posed by both the HBV and COVID-19 pandemics, our findings may have significant implications for dually infected individuals and for public health efforts aimed at addressing both epidemics.

Our analysis of baseline characteristics showed that, compared with individuals with SARS-CoV-2 alone, those with HBV/SARS-CoV-2 had a 2- to 10-fold higher prevalence of comorbid conditions and lifestyle-associated risk factors. These included older age, overweight/obesity, cirrhosis and other disease of liver, cardiovascular diseases, diabetes, chronic lung diseases, chronic kidney diseases, malignancies, organ transplants, nicotine-related disorders, and alcohol-related disorders. Moreover, the HIV and HCV coinfection rates were more than 20- and 30-fold higher, respectively, in this group compared with the SARS-CoV-2–only group. These comorbidities are recognized as major contributors to severe outcomes in SARS-CoV-2 infection, including death and the postacute sequelae of SARS-CoV-2 [19–23].

Following propensity score matching, the disparity in most comorbidities between the groups was eliminated, including overall chronic liver disease; however, individuals with HBV/SARS-CoV-2 remained significantly more likely to have cirrhosis. Sensitivity analyses further confirmed that individuals with HBV/SARS-CoV-2 and concomitant cirrhosis had 2.0- to 2.5-fold higher odds of poor outcomes compared to the SARS-CoV-2–only group. These findings are consistent with previous studies that have identified cirrhosis specifically as a major determinant of SARS-CoV-2 severity and outcomes [4–7]. Notably, despite no observed differences in 30-day and 90-day mortality for individuals with HBV/SARS-CoV-2 without cirrhosis, we observed increased odds of adverse outcomes, specifically mechanical ventilation and all-cause mortality, when compared to the SARS-CoV-2-only cohort. This suggests a role for HBV-specific mechanisms likely related to chronic proinflammatory responses and immune dysregulation [24, 25]. Although these effects are likely to be primarily hepatic, they may extend to extrahepatic tissues and potentially work in synergy with the SARS-CoV-2–induced cytokine storm, contributing to the high rates of end-organ damage observed in SARS-CoV-2 disease [24, 25].

Laboratory abnormalities are well-recognized in COVID-19, particularly in individuals with underlying liver disease, and often reflect multiorgan dysfunction in severe cases [26, 27]. In the subset of individuals with baseline laboratory data obtained within 30 days after SARS-CoV-2 diagnosis, those with HBV/SARS-CoV-2 coinfection were significantly more likely to have anemia, thrombocytopenia, renal impairment, hyperglycemia, coagulopathy, dyslipidemia, alveolar damage (evidenced by elevated lactate dehydrogenase), and hepatic injury (indicated by elevated liver function tests) compared to the SARS-CoV-2–only cohort. Of particular interest, abnormalities in liver enzymes are recognized as a feature of severe SARS-CoV-2, with studies reporting between 14.8% and 53% of individuals with moderate or severe

SARS-CoV-2 show abnormalities in liver enzymes during the acute phase of the illness [28]. A study from China showed that after 2 weeks of hospitalization, individuals with SARS-CoV-2 with abnormal liver function tests increased to 76.3% [29]. In the present study, individuals with chronic HBV infection comparatively had significantly higher levels of liver transaminases, hyperbilirubinemia, and hypoalbuminemia. However, these findings likely represent a subgroup of hospitalized individuals or those with more severe SARS-CoV-2 or HBV disease, as opposed to individuals with milder illness managed in outpatient settings. This nuance is critical for contextualizing the results within the broader spectrum of COVID-19 severity.

The etiology of hepatic injury in SARS-CoV-2 in the context of underlying HBV infection may involve multiple pathophysiologic processes. First, studies have confirmed the hepatotropism of SARS-CoV-2, with its cellular receptor ACE2 abundantly expressed on hepatocytes, Kupffer cells, hepatic endothelial cells, and cholangiocytes [3], suggesting a direct viral cytopathic effect in SARS-CoV-2–induced liver injury [3, 10]. Upon entry into the cell, SARS-CoV-2 activates mTOR signaling and impairs autophagy, which results in immune evasion and liver injury through mitochondrial dysfunction and oxidative stress [30, 31]. Second, drug-induced liver injury has been reported in 10% to 63% of cases resulting from a wide array of drugs used in the management of SARS-CoV-2, including antivirals (eg, remdesivir, lopinavir-ritonavir), corticosteroids (eg, dexamethasone, methylprednisolone), monoclonal antibodies (eg, tocilizumab, tofacitinib), nonsteroidal anti-inflammatory drugs, and antibiotics [12, 32, 33]. Third, several studies have reported HBV reactivation in SARS-CoV-2 infection, with higher rates observed in individuals with positive hepatitis B surface antigen compared to those with negative hepatitis B surface antigen/hepatitis B core antibody test–positive status [13]. This phenomenon appears to be linked to immunosuppressants such as corticosteroids (especially methylprednisolone) and tocilizumab [13, 33–35]. Consequently, HBV screening and antiviral prophylaxis with tenofovir or entecavir have been suggested for high-risk individuals before receiving high-dose immunosuppressants in SARS-CoV-2 disease [35, 36]. Of note, individuals in the HBV/SARS-CoV-2 group were significantly more likely to be treated with corticosteroids and other SARS-CoV-2 treatments compared to those with SARS-CoV-2 only, which could have contributed to liver damage and the poor clinical outcomes observed in this group.

Furthermore, individuals with HBV/SARS-CoV-2 in our study had significantly higher levels of systemic inflammatory markers, such as CRP, ESR, ferritin, and procalcitonin, but not IL-6 levels. In severe SARS-CoV-2 infection, the activation of host SARS-CoV-2–specific CD4+/CD8+ T-cell responses leads to the overproduction of the pro-inflammatory cytokines IL-1, IL-6, and tumor necrosis factor-α, which are the main drivers of the viral cytokine storm [11]. In particular, IL-6 has been linked to severe hepatic injury and is correlated with poor prognosis in severe SARS-CoV-2 [37]. It has also been suggested that in HBV/SARS-CoV-2 coinfection, HBV-specific CD4+/CD8+ T-cell responses may amplify the cytokine storm and contribute to severe disease [24, 25]; however, this assertion remains controversial. Chronic HBV infection is characterized by persistence of the HBV viral reservoir in the form of covalently closed circular DNA. This ultimately results in HBV-specific CD4+/CD8+ T-cell exhaustion, a phenomenon marked by diminished effector responses and reduced secretion of proinflammatory cytokines, which would be expected to dampen rather than exacerbate the cytokine storm [38–40]. Conversely, it has been proposed that in mild/moderate SARS-CoV-2 infection, HBV-specific CD4+/CD8+ T-cell exhaustion could orchestrate the exhaustion of natural killer and SARS-CoV-2–specific CD4+/CD8+ T cells, leading to the upregulation of inhibitory immune checkpoints (IC) such as *PD-1, CTLA-4, TIM-3, NKG2A, LAG3, VISTA*, and *Gal-9* [25, 39–41]. Inhibitory ICs, which usually downregulate the immune response to prevent excessive inflammation, contribute to T-cell exhaustion [41]. This impairs virus elimination, leading to a prolonged and dysregulated immune response and worsening disease severity [41]. Notably, the upregulation of ICs has also been linked to CD8+ T cell–mediated apoptosis, which has been linked to lymphopenia and other hematological abnormalities observed in severe SARS-CoV-2 [42–44].

We also showed in subgroup analysis of individuals with HBV/SARS-CoV-2 that those who received any dose of the SARS-CoV-2 vaccine had a 57%, 54%, and 29% reduction in 30-day, 90-day. and overall mortality, respectively, compared with those who were unvaccinated. Currently available SARS-CoV-2 vaccines have demonstrated efficacy in reducing disease severity, as well as hospitalization, ICU admission, and mortality rates in the general population [45–47]. The CDC recommends prioritizing SARS-CoV-2 vaccination for individuals with chronic medical conditions, including chronic liver disease and HBV infection, due to their increased risk for severe COVID-19 outcomes [48]. However, concerns about SARS-CoV-2 vaccine effectiveness persist in immunocompromised individuals, such as people with HIV with lower CD4 counts and those with organ transplants and malignancies, who are at risk of diminished vaccine responses and may require additional vaccine doses to achieve effective immunity [49, 50]. It has similarly been hypothesized that the aberrant immune response seen in HBV/SARS-CoV-2 coinfection may lead to suboptimal SARS-CoV-2 vaccine efficacy in this population; however, few studies have investigated the potential impact of SARS-CoV-2 vaccination on disease severity and outcomes in individuals with chronic HBV infection specifically. Our results demonstrate that SARS-CoV-2

vaccination is effective in preventing adverse outcomes individuals with chronic HBV infection. Given the heightened risks of severe COVID-19 in this population, our results underscore the importance of adhering to the CDC advice to prioritize SARS-CoV-2 vaccination for individuals with underlying chronic liver disease.

Interestingly, SARS-CoV-2 outcomes in individuals with chronic HBV infection were not significantly affected by the SARS-CoV-2 variant type in circulation, except for higher hospitalization rates in the pre-Delta era compared with the Omicron era. Different SARS-CoV-2 variants carry varying risks for severe disease. Generally, Omicron variants are considered less lethal than earlier variants, despite being more transmissible and immune-evasive [51]. In the United States, the Omicron variants became predominant by late December 2021 [51, 52]. Despite the initial peak of the Omicron wave in the United States coinciding with an increase in emergency room visits, hospitalizations, and deaths, this trend subsequently saw a reversal [51, 52], consistent with the overall observations of our study.

Several limitations should be considered in interpreting the findings of this study. First, reliance on electronic health record data introduces potential biases, including variations in data quality and completeness, as well as limitations associated with using ICD-10 codes for diagnoses. This approach may lead to misclassification, and diagnoses not accurately recorded could be missed, a common challenge in observational studies. Second, the retrospective nature of the study design limits causal inference, and despite the use of propensity score matching, unmeasured confounders may still influence the results. Third, the generalizability of the findings may be restricted to the study's geographical scope and healthcare organizations involved. Additionally, the study does not account for the potential impact of specific antiviral treatments on outcomes. Our analysis on SARS-CoV-2 variants relied on the predominant circulating variants in the United States at the time rather than direct testing of variants in study participants. Despite these limitations, the study offers valuable insights into the complex interplay between chronic hepatitis B virus and SARS-CoV-2 outcomes.

In summary, chronic HBV infection was associated with higher odds of mortality and adverse outcomes in SARS-CoV-2 infection, driven in large part by a high burden of underlying chronic liver disease and other comorbidities. Importantly, SARS-CoV-2 vaccination was associated with a significant reduction in the odds of death and the need for ICU admission, suggesting that vaccination could be an effective strategy for mitigating the impact of SARS-CoV-2 in individuals with chronic HBV infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. G.A.Y. conceptualized the study. G.A.Y. curated the data and conducted the statistical analysis. G.A.Y., T.O., F.M., R.A.S., A.M.M., and J.M.J. were responsible for the methods, formal analysis, and visualization. G.A.Y. acquired the funding and was responsible for project administration. G.A.Y. wrote the original draft. All authors reviewed and edited the manuscript and provided important intellectual content. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Data Sharing. Deidentified individual participant data that underlie the results were extracted from TriNetX, a federated national health research network with data sourced from 97 health care organizations (HCO) within the United States with waiver from WCG IRB.

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