

Effect of SARS-CoV-2 Infection on HBV-Infected Patients: Reactivation

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Abstract

Background: Hepatic manifestations of COVID-19 are prevalent in individuals infected with viral hepatitis type B (HBV). **Objectives:** The current study aims to determine the extent of the HBV reactivation depending on the immune impact on patients infected with SARS-CoV-2. **Materials and Methods:** One hundred forty-one hospitalized cases were divided into patients infected with HBV with/without SARS-CoV-2 diagnosed by automatic fluorescent immunoassay system COVID-19 Ab (IgM/IgG). Next, HBV reactivation was assessed using hepatitis B surface antigen (HBsAg), HBcAb (IgM), HBeAg, and HBeAb ELISA test. **Results:** The results showed significant differences in HBV reactivation patients with SARS-CoV-2 at $P < 0.05$. Out of 141 HBV patients, 115 (1, 80, and 34) had positive COVID-19 in IgM, IgG, and IgM with IgG, respectively. The results of reactivation test showed 34.07% of patients have HBV reactivation. **Conclusions:** The HBV reactivation patients had been recorded in acute and chronic cases of HBV patients, where no severe cases were recorded compared with the advanced cases of the disease who received immunosuppressive therapy and biological treatment. Therefore, it is necessary to consider the special care of persons exposed to infection with SARS-CoV-2 to patients infected with viral hepatitis, in particular, advanced cases of the disease and their stages of treatment as it leads to liver dysfunction and life-threatening complications.

Keywords: Coinfection, HBV, HBV reactivation, SARS-CoV-2

INTRODUCTION

Since January 2022, the number of infections with SARS-CoV-2 began to be limited globally. However, soon the cases rose by 8% during the first 2 weeks of March 2022, reaching 11 million new infections and 43,000 deaths, bringing the total infections to more than 445 million confirmed cases and more than 6 million deaths universal as of March 13, 2022. Therefore, this disease is still considered a pandemic.^[1] Most of the people who test positive for COVID-19 develop mild or no symptoms, whereas others develop acute respiratory distress syndrome, heart failure, blood clots, neurological complications, and elevated inflammatory response.^[2-5]

Hepatitis B virus (HBV) infection is a global public health problem. The frequency distribution of HBV genotypes in Iraqi patients was recorded by several authors.^[6] The prevalence of this infection has increased among many patients with other diseases.^[7-10]

People infected with HBV may develop coinfection such as SARS-CoV-2, which can affect patients and cause HBV reactivation, indicating significant disruptions between the host's immune system and viral replication.^[11]

The severity of immunosuppressive treatments is also the leading risk factor for HBV reactivation. For example, HBV reactivation in patients with SARS-CoV-2 is commonly related to immunosuppressive therapy such as an IL-1 or IL-6 receptor antagonist (anakinra and tocilizumab) and high doses from corticosteroids.^[12,13]

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A decreased liver cell functioning is linked to chronic liver disease (CLD). As a result, medicines that undergo hepatic metabolism will be less effective in CLD patients.^[14] The cytochrome P450 (CYP) enzyme is the primary metabolizer of most medicines.^[15-19] Several earlier investigations have shown that liver illness has a varied influence on the CYP activity.^[17,20]

Moreover, abnormal outcomes in liver function tests (LFT) are observed in people infected with SARSCoV-2 alone or SARS-CoV-2 with HBV or in people with HBV alone. These abnormal outcomes were also observed according to reports of HBV reactivation in patients infected with SARS-CoV-2. A retrospective study found three out of 21 patients with coinfection with SARS-CoV-2 and HBV; thus, two received corticosteroid therapy due to developed HBV reactivation.^[21] The most prospective study assessed the risks of HBV reactivation in hepatitis B surface antigen (HBsAg)-negative/HBcAb-positive patients with severe SARS-CoV-2 infection receiving immunosuppressive therapy.^[13] At 1-year follow-up, there was no HBsAg seroconversion, and two out of 69 seropositive HBV subjects had detectable DNA, representing a lower risk of HBV reactivation in patients with severe cases of SARS-CoV-2 and resolving HBV infection.^[22]

Previous studies indicate that elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are observed in approximately 20% of COVID-19 patients,^[23,24] with AST levels often higher than ALT during the disease.^[25] The cause of this LFT pattern is not fully elucidated but does not appear to be related to muscle breakdown or hepatic ischemia. In addition, elevated gamma-glutamyl transferase and total bilirubin are reported in 23% and 1%–18% of patients, respectively, whereas the elevation of alkaline phosphatase is less common, occurring in 2%–5% of patients.^[23,24] Moreover, liver cirrhosis is also associated with higher COVID-19-related mortality.^[26]

In addition to those with HBV infection (HBsAg-positive), there are two billion people globally with past or resolved HBV infection, so HBsAg negative with HBcAb positive.^[27] In a previous study, chronic HBV with SARS-CoV-2 coinfection was recorded in Asia at about 0.8%–6.3% compared with 0.1% in the United States.^[28]

The COVID-19 pandemic has stopped routine healthcare services in most cases of other illnesses, including HBV infection, and thus, screening and monitoring are required before and after treatment. In a study conducted by Mandel *et al.*,^[29] to determine the influence of the pandemic on HBV testing in Ontario/Canada, the first wave of the pandemic was observed in April 2020 and it recovered to 72%–75% of prepandemic volumes by the end of the first wave of the pandemic. As a result, the HBsAg test decreased by 33%, 18%, and 15%, and the HBV DNA test decreased by 37%, 27%, and 20% in each successive

wave. Thus, these data provide insight into the epidemic's effects on the examination and treatment of other diseases that may have consequences that are difficult to observe, especially with patients with advanced cases. Therefore, the current study aims to determine the extent of the HBV reactivation depending on the immune impact in patients infected with SARS-CoV-2.

MATERIALS AND METHODS

Study design

In this case-control study, 141 blood specimens were obtained from confirmed HBV patients in the Hepatology and Gastroenterology Teaching Hospital in Baghdad Medical City from March to June 2021. All 141 hospitalized cases were divided into two groups: the first group included patients infected with HBV (noninfected with SARS-CoV-2), whereas the second group included patients with HBV (infected with SARS-CoV-2). Automatic fluorescent immunoassay system (AFIAS) COVID-19 Ab (IgM/IgG) tests were used for classifying all studied subjects.

All cases enrolled in this study were according to the following inclusion criteria: patients with HBV and primary viral hepatitis, and also patients undergoing blood transfusion, hemodialysis, autoimmune diseases, and HBV contact, in addition to some illnesses that accompanied patients' confirmed cases, such as blood pressure, diabetes, rheumatoid arthritis, leukemia, thalassemia, renal failure, bone marrow graft, and lymphadenopathy.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with the patients' verbal approval before the sample was taken. The study protocol and patient consent forms were reviewed and approved by Baghdad Health Directorate and the Committee on Publication Ethics at the College of Medicine, University of Babylon, Iraq, under reference no. BMS/0298/016 (dated February 12, 2021).

Specimens' collection

Three to five milliliters of blood specimens from all subjects in the study was drawn, using sterile 20-mL syringes with sterile needle G-22 for persons with HBV diagnosed previously clinically. In addition, sterile 10 mL capacity sterile gels were labeled with number codes and information were recorded according to the case information sheet. After that, the immunological test was performed.

Detection of HBV reactivation

Diagnostic kits for HBV were used for testing all specimens by AFIAS (COVID-19 Ab [IgM/IgG] test, Boditech Med Inc., Korea) and enzyme-linked immunosorbent assay

(HBsAg and HBcAb [IgM] ELISA Kit, InTec Products, Inc., Xiamen, China, and HBeAg and HBeAb ELISA Kit, ACON Laboratories, Inc., San Diego, USA) in human serum or plasma. Parameters were measured according to the instruction of the manufacturing company.

In addition, HBV reactivation was assisted based on the study by Aldhaleei *et al.*,^[30] which indicated HBsAg positivity, HBcAb (IgM) positivity, HBeAg negativity, and HBeAb positivity, which are suggestive of HBV reactivation patients infected with SARS-CoV-2.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 26 (SPSS Inc., Chicago, IL, USA). The analysis of difference (ANOVA), independent sample T-test for measuring the differences between two groups, and chi-square (X^2) for categorical data were used. P value > 0.05 was set as significant (95%).

RESULTS

HBV infection and SARS-CoV-2 coinfection

To investigate consequences on patients' susceptibility to SARS-CoV-2 coinfections, so through the case information and before conducting the SARS-CoV-2 test for individuals infected with HBV, 39 out of 141 individuals were confirmed positive for SARS-CoV-2 infection by RT-PCR, CT scan, and other tests currently used for the diagnosis of this disease.

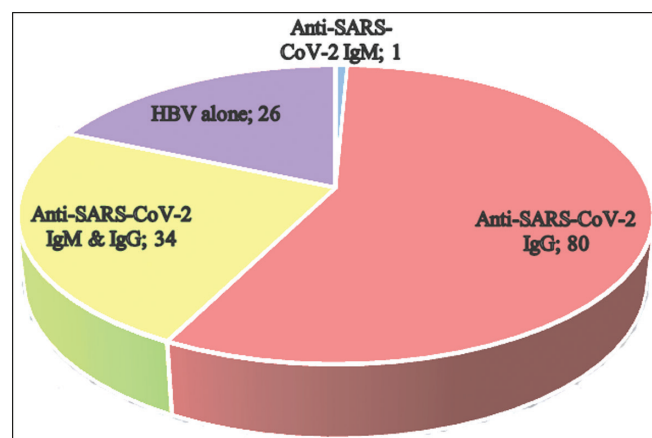


Figure 1: Patients' HBV infection and SARS-CoV-2 coinfection with anti-SARS-CoV-2

However, all patients included in the present study were unvaccinated for COVID-19 because the vaccination program in Iraq was started after sample collection and after conducting immunological experiments.

The serodiagnosis of anti-SARS-CoV-2 is described in Figure 1, depending on the previous description in item four above methodology. The results showed that only one HBV patient (0.7%) had positive COVID-19 IgM, 80 out of 141 HBV patients (56.7%) gave positive results for COVID-19-IgG antibodies, and 34 out of 141 HBV patients (24.1%) gave positive results for both COVID-19-IgM and IgG antibodies. In contrast, HBV-infected patients' sera showed only 26 out of 141 (18.4%) were negative for both COVID-19-IgM and IgG antibodies (HBV alone).

Regarding the 39 patients who were confirmed as SARS-CoV-2 positive (by RT-PCR, CT scan, and other tests currently used for the diagnosis of this disease) before conducting the anti-SARS-CoV-2 test, 48.7% of patients were positive for anti-SARS-CoV-2, IgG [Figure 1].

HBV infection distribution and SARS-CoV-2 coinfection

Patient's gender and age groups

A hundred and forty-one HBV patients were enrolled in this study. They included 80 (56.74%) males and 61 (43.26%) females. As shown in Table 1, males had a higher incidence of sex-related coinfection of HBV-infected patients than females, 48.9% and 32.6%, respectively. Thus, the male:female ratio in cases of HBV and SARS-CoV-2 was equal to 1:1.5, whereas in cases of HBV alone, it was equal to 1:0.73.

The patients were divided into three groups for the subject of HBV with SARS-CoV-2 and HBV alone infected according to the age. These groups ranged from lower than 30 years to greater than 60 years. The results revealed that most of the patients in the second group were between 30 and 60 years, with a percentage of 49.6%, and the lowest in the third group with age greater than 60 years as the ratio was 6.4% compared with the control (HBV alone) groups [Table 2].

HBV vaccine received

According to the vaccination status of HBV infection, the results are described in Table 3. The results revealed that 5.7% vaccinated for HBV have confirmed cases of HBV

Table 1: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to gender

Groups	Gender	Frequency	%	P value
HBV and SARS-CoV-2	Male	69	48.9	0.024
	Female	46	32.6	
HBV alone	Control male	11	7.8	0.043
	Control female	15	10.6	
Total		141	100.0	

Table 2: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to age groups

Groups	Age	Frequency	%	P value
HBV and SARS-CoV-2	Young (<30 years)	36	25.5	0.008
	Adult (30–60 years)	70	49.6	
	Elderly (>60 years)	9	6.4	
HBV alone	Control young (<30 years)	10	7.1	0.046
	Control adult (30–60 years)	14	9.9	
	Control elderly (>60 years)	2	1.4	
Total		141	100.0	

Table 3: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to HBV vaccine received

HBV vaccine received	Infection	Frequency	%	P value
Vaccinated	HBV with SARS-CoV-2	8	5.7	<0.001
	HBV alone	4	2.8	
Nonvaccinated	HBV without SARS-CoV-2	107	75.9	
	HBV alone	22	15.6	
Total		141	100.0	

Table 4: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to HBV contact

Groups	HBV contact	Frequency	%	P value
HBV and SARS-CoV-2	House contact	37	26.2	<0.001
	Work contact	3	2.1	
	Others	75	53.2	
HBV alone	House contact	7	5.0	
	Work contact	0	0.0	
	Others	19	13.5	
Total		141	100.0	

with SARS-CoV-2 compared to HBV alone, 2.8%. In addition, the results showed that 75.9% of nonvaccinated HBV have confirmed cases of HBV with SARS-CoV-2 compared to HBV alone at 15.6%.

HBV contact

The data in Table 4 showed the distribution of HBV alone and HBV with SARS-CoV-2 patients according to the HBV contact. Among 141 subjects of the study, HBV contact was studied as a demographic distribution, and the results presented that the percentage of house contact in the study was 26.2%.

Diseases status

This study revealed that chronic HBV was more frequent in the status of the diseases (58.2%), whereas acute, chronic active, and autoimmunity (17%, 3.5%, and 2.8%, respectively) were associated with SARS-CoV-2 and HBV patients. Also, the chronic status disease was 12.8% among patients with HBV alone [Table 5].

Liver cirrhosis

The results of HBV alone and HBV with SARS-CoV-2 are described in Table 6 according to liver cirrhosis. The

results revealed that in HBV patients infected with SARS-CoV-2, five out of 141 (3.5%) with cirrhosis compared with patients without cirrhosis, 110 (78%). In contrast, nonpatients (0.00%) only had cirrhosis in the HBV infection group.

HBV reactivations

The results in Table 7 showed the distribution of HBV alone and HBV with SARS-CoV-2 patients according to HBV reactivation. Fifty patients did not undergo testing by ELISA selectively as it had nearly similar values to the tested patient's sera. The current study showed significant differences among HBV with SARS-CoV-2, reactivation, HBV with SARS-CoV-2, nonreactivation, and HBV alone (34.07%, 37.36%, and 28.57%, respectively).

Distribution of SARS-CoV-2 with immunological markers according to sociodemographic and predisposing factors

In the present study, the distribution of SARS-CoV-2 with immunological markers in HBV-infected patients according to some sociodemographic factors (gender and age) and predisposing factors (HBV vaccine received, diseases status, HBV contact, and liver cirrhosis) was

Table 5: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to diseases status

Groups	Diseases status	Frequency	%	P value
HBV and SARS-CoV-2	Acute	24	17.0	<0.001
	Chronic	82	58.2	
	Chronic active	5	3.5	
	Autoimmunity	4	2.8	
HBV alone	Acute	3	2.1	
	Chronic	18	12.8	
	Chronic active	3	2.1	
	Autoimmunity	2	1.4	
Total		141	100.0	

Table 6: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to liver cirrhosis

Groups	Liver cirrhosis	Frequency	%	P value
HBV and SARS-CoV-2	With cirrhosis	5	3.5	<0.001
	Without cirrhosis	110	78.0	
HBV alone	With cirrhosis	0	0.0	
	Without cirrhosis	26	18.4	
Total		141	100.0	

Table 7: Patients' HBV infection distribution and SARS-CoV-2 coinfection according to HBV reactivations

Reactivation	No. of cases	%	% of the total 91 samples tested	P value
HBV alone	26	18.4	28.57	0.027
HBV with SARS-CoV-2, reactivation	31	22.0	34.07	
HBV with SARS-CoV-2, nonreactivation	34	24.1	37.36	
HBV with SARS-CoV-2, ND*	50	35.5	-	
Total	141	100.0	100.0	

*ND = not determined

studied. The results in Table 8 showed significant differences among gender, HBV vaccine received, HBV contact, and liver cirrhosis. On the other hand, there was no significant difference between age and disease status for IgM compared with the control group. However, IgG results showed very significant differences in all demographic distributions compared to the control group.

Regarding HBV reactivation [Table 9] for the two study groups and HBV-infected subjects, the results showed that HBsAg, HBcAb (IgM), and HBeAg in all sociodemographic factors and predisposing factors have significant differences compared to the control group. As for HBeAb, significant differences were seen in the disease status, HBV contact, and liver cirrhosis. In contrast, compared to the control group, no significant differences were found among patients regarding gender, age, and vaccine.

DISCUSSION

Since the COVID-19 pandemic, many studies have begun on the SARS-CoV-2 regarding disease mechanism, ways of spreading, and its impact on coinfection, especially among individuals with transmissible diseases, including HBV. Therefore, in the current study, we used previously

confirmed specimens for HBV infection by using the RT-PCR technique and recorded them in the patient's information case sheet. In addition, IgM and IgG SARS-CoV-2 were considered as a coinfection because some investigators reported that IgM Abs could be detected 3 days after post-COVID-19-infection as the first line of humoral immunity followed by IgG antibodies after 7 days.^[31]

In the meanwhile, no population dealing with these subjects has been found currently, and no similar related research was found in the current publication.

The current results indicated that the gender of the infected person plays an essential role in the predisposition to infection with viral diseases. This study's results showed significant differences in infections among males and females. The present study is the first trial to study the correlation between HBV with SARS-CoV-2 and HBV alone. Yet all previous studies had been directed at studying HBV infection. The current results were consistent with the findings obtained by the study of Williams and Wilkins,^[32] which found that the infection rates were higher in males than in females, and in addition to other studies conducted in Iraq, such as the study of

Table 8: Comparison of SARS-CoV-2 demography with anti-SARS-CoV-2 in HBV-infected patients

Properties		COVID-19			
		IgM (mIU/mL)		IgG (mIU/mL)	
		Mean $\pm$ SD	P value	Mean $\pm$ SD	P value
Gender	Male*	0.8429 $\pm$ 0.86076	0.016	4.8149 $\pm$ 2.55139	<0.001
	Female*	0.7485 $\pm$ 0.67222		4.8711 $\pm$ 2.49602	
	Control male**	0.2936 $\pm$ 0.12484		0.5036 $\pm$ 0.37644	
Age	Control female**	0.3087 $\pm$ 0.23522	0.072	0.3313 $\pm$ 0.41993	0.005
	Young (<30 years)*	0.7972 $\pm$ 1.10483		5.3075 $\pm$ 2.86983	
	Adult (30–60 years)*	0.8010 $\pm$ 0.61795		4.7981 $\pm$ 2.34911	
	Elderly (>60 years)*	0.8689 $\pm$ 0.48113		3.2622 $\pm$ 1.72049	
	Control young (<30 years)**	0.2300 $\pm$ 0.08589		0.3450 $\pm$ 0.44754	
	Control adults (30–60 years)**	0.3629 $\pm$ 0.24085		0.4593 $\pm$ 0.39970	
HBV vaccine received	Control elderly (>60 years)**	0.2400 $\pm$ 0.00000	0.011	0.3150 $\pm$ 0.31820	<0.001
	Vaccinated*	0.5912 $\pm$ 0.35454		5.0750 $\pm$ 3.09790	
	Nonvaccinated*	0.8212 $\pm$ 0.80704		4.7824 $\pm$ 2.50502	
	Nonvaccinated**	0.2919 $\pm$ 0.17145		0.4071 $\pm$ 0.40069	
Diseases status	Vaccinated**	0.2250 $\pm$ 0.74285	0.053	0.2900 $\pm$ 0.46698	<0.001
	Acute*	0.7948 $\pm$ 0.47828		4.4356 $\pm$ 2.85895	
	Chronic*	0.8056 $\pm$ 0.89180		4.9437 $\pm$ 2.49361	
	Chronic active*	0.6740 $\pm$ 0.31230		3.5560 $\pm$ 2.11801	
	Autoimmunity*	0.8675 $\pm$ 0.56252		5.5750 $\pm$ 2.07285	
HBV contact	Control**	0.3072 $\pm$ 0.19540	0.012	0.4184 $\pm$ 0.40537	<0.001
	House contact*	0.7130 $\pm$ 0.60036		5.1589 $\pm$ 2.46980	
	Work contact*	1.0200 $\pm$ 0.49508		5.1467 $\pm$ 3.15611	
	Others*	0.8420 $\pm$ 0.87721		4.6664 $\pm$ 2.53961	
Liver cirrhosis	Control**	0.3023 $\pm$ 0.19307	0.02	0.4042 $\pm$ 0.40369	<0.001
	With cirrheses*	0.2880 $\pm$ 0.16724		4.2560 $\pm$ 2.40043	
	Without cirrheses*	0.8286 $\pm$ 0.79824		4.8638 $\pm$ 2.53105	
		Control**	0.3023 $\pm$ 0.19307	0.4042 $\pm$ 0.40369	

*HBV and SARS-CoV-2

**HBV alone

Marhoon,^[33] which was carried on 188 and reported that males (115) are more than females (66).

A study conducted in Najaf governorate, Iraq, showed that the prevalence of HBV among 1305 blood donors (during 2017–2018) was 3%, and most of the seropositive donors were HBV positive (84.3%).^[34]

Othman and Abbas^[35] studied HBV among 634 patients during 2015–2019 in Thi-Qar Province, Iraq, and they found high infection rates among males compared with females. In addition, Alhajji^[36] mentioned that males had a higher infection compared with females.

The reason is that males represent the most significant proportion of mixing with the external environment and are more socially active because of Arab cultures, especially in Iraq, which point of view equals the number of infections among countries with open cultures, such as European countries, for example, in addition to some tradition that is allowed by society for males without females, such as cupping (Chinese medicine), which simple people from the general community practice, which is considered one of the important ways to transmit disease,

the possibility of narcotics and alcohol consumption, the possibility of males engaging in illegal relationships, and other reasons that could be through the everyday use of razors and razors in shaving shop, and males are more than females to travel. Hence, the incidence of males is more than females.

Previous comparative studies on males and females in the last 18 years revealed that females were more resistant to viral infection. This is because they had less infection exposure than males and higher cellular and humoral immune response and innate immune response levels. In addition, females possess more CD4+ T-cell and cytotoxic T lymphocytes than males. Thus, it stimulates a more significant number of T cells activated by the interaction of viral antigens with the T-cell receptors according to CD4+ T-cell, compared to cytotoxic T lymphocytes that were more potent activity combined with the overexpression of antiviral and proinflammatory genes, many of which contain hormone estrogen response elements in their promoters that have been reported in women, so it is unacceptable that females are less susceptible viruses than males because of their more effective antiviral immune defenses.^[37]

Table 9: Comparison of SARS-CoV-2 demography with reactivation markers in HBV-infected patients

Properties		Reactivation							
		HBsAg (IU/mL)		HBcAb (IgM) (IU/mL)		HBeAg (IU/mL)		HBeAb (IU/mL)	
		Mean $\pm$ SD	P value	Mean $\pm$ SD	P value	Mean $\pm$ SD	P value	Mean $\pm$ SD	P value
Gender	Male*	0.5797 $\pm$ 0.52597	0.020	0.5942 $\pm$ 0.55090	0.019	0.9275 $\pm$ 0.89638	0.065	0.6812 $\pm$ 0.67503	0.206
	Female*	0.6304 $\pm$ 0.60951		0.6522 $\pm$ 0.64005		0.9565 $\pm$ 0.91788		0.6739 $\pm$ 0.66848	
	Control**	0.9231 $\pm$ 0.39223		0.9615 $\pm$ 0.44549		1.3846 $\pm$ 0.69725		0.9231 $\pm$ 0.39223	
Age	Young (<30 years)*	0.7500 $\pm$ 0.60356	0.008	0.7500 $\pm$ 0.60356	0.015	1.1389 $\pm$ 0.89929	0.037	0.7222 $\pm$ 0.56625	0.334
	Adult (30–60 years)*	0.5286 $\pm$ 0.53083		0.5571 $\pm$ 0.58075		0.8286 $\pm$ 0.88418		0.6571 $\pm$ 0.72002	
	Elderly (>60 years)*	0.5556 $\pm$ 0.52705		0.5556 $\pm$ 0.52705		1.0000 $\pm$ 1.00000		0.6667 $\pm$ 0.70711	
	Control**	0.9231 $\pm$ 0.39223		0.9615 $\pm$ 0.44549		1.3846 $\pm$ 0.69725		0.9231 $\pm$ 0.39223	
HBV vaccine received	Vaccinated*	1.0000 $\pm$ 0.53452	0.003	0.8750 $\pm$ 0.35355	0.030	1.5000 $\pm$ 0.75593	0.046	1.1250 $\pm$ 0.64087	0.064
	Nonvaccinated*	0.5741 $\pm$ 0.55034		0.6019 $\pm$ 0.59499		0.9074 $\pm$ 0.90210		0.6481 $\pm$ 0.66014	
	Nonvaccinated**	0.8571 $\pm$ 0.35857		0.9524 $\pm$ 0.49761		1.3810 $\pm$ 0.74001		0.9048 $\pm$ 0.43644	
	Vaccinated**	1.2500 $\pm$ 0.50000		1.0000 $\pm$ 0.00000		1.2500 $\pm$ 0.50000		1.0000 $\pm$ 0.00000	
Diseases status	Acute*	0.49329 $\pm$ 0.09866	<0.001	0.53852 $\pm$ 0.10770	0.001	0.75719 $\pm$ 0.15144	0.004	0.61101 $\pm$ 0.12220	0.004
	Chronic*	0.52690 $\pm$ 0.05819		0.57185 $\pm$ 0.06315		0.88923 $\pm$ 0.09820		0.64974 $\pm$ 0.07175	
	Chronic active*	0.83666 $\pm$ 0.37417		0.54772 $\pm$ 0.24495		1.09545 $\pm$ 0.48990		0.54772 $\pm$ 0.24495	
	Autoimmunity*	0.50000 $\pm$ 0.25000		0.50000 $\pm$ 0.25000		0.95743 $\pm$ 0.47871		0.81650 $\pm$ 0.40825	
	Control**	0.40000 $\pm$ 0.08000		0.45461 $\pm$ 0.09092		0.70711 $\pm$ 0.14142		0.40000 $\pm$ 0.08000	
HBV contact	House contact*	0.7568 $\pm$ 0.59654	0.002	0.7838 $\pm$ 0.62960	0.002	1.1622 $\pm$ 0.89795	0.002	0.7838 $\pm$ 0.62960	0.034
	Work contact*	1.0000 $\pm$ 0.00000		1.0000 $\pm$ 0.00000		2.0000 $\pm$ 0.00000		1.3333 $\pm$ 0.57735	
	Others*	0.5067 $\pm$ 0.52949		0.5200 $\pm$ 0.55410		0.7867 $\pm$ 0.87446		0.6000 $\pm$ 0.67783	
	Control**	0.9231 $\pm$ 0.39223		0.9615 $\pm$ 0.44549		1.3846 $\pm$ 0.69725		0.9231 $\pm$ 0.39223	
Liver cirrhosis	With cirrhoses*	0.2000 $\pm$ 0.44721	0.005	0.2000 $\pm$ 0.44721	0.005	0.4000 $\pm$ 0.89443	0.024	0.2000 $\pm$ 0.44721	0.045
	Without cirrhoses*	0.6182 $\pm$ 0.55821		0.6364 $\pm$ 0.58619		0.9636 $\pm$ 0.89778		0.7000 $\pm$ 0.67116	
	Control**	0.9231 $\pm$ 0.39223		0.9615 $\pm$ 0.44549		1.3846 $\pm$ 0.69725		0.9231 $\pm$ 0.39223	

*HBV and SARS-CoV-2

**HBV alone

The current studies showed significant differences in the incidence of infection in different age groups studied. For example, Table 2 shows that adults (30–60 years) have recorded the highest infection rate compared with other age groups.

When comparing the results of this study with other Iraqi studies, it was found that Ataei *et al.*^[38] obtained compatibility with the results as they found that HBV infection was significantly higher among (<60 years) older patients. They suggested that the high rate of HBV infection among older patients may be due to the length of exposure to the virus and the sexual activity.

The present result showed that the patients less than 20-years-old composed the third high group. This result was incompatible with Al-Thwani *et al.*, who pointed out that the highest prevalence of HBsAg had been seen in the age group of 15–20 years.^[39] Furthermore, the result of the current study was in contrast with Marhoon^[33] who found that most of the patients were within the age group of 20–30 years (29.83%) and of more than 50 years (26.52%). They also observed that the age groups 31–40 years and 41–50 years were 13.26% and 19.89%, respectively. Hence, his result concluded that the age of infection varied

according to geographical area and period of sample collection. The present results coincide with the previous studies done in Iraq by Al-Waysi,^[40] who concluded that 30–60 years was the mean age for chronic hepatitis B patients, and another study conducted in Iraq by Hanash,^[41] who found that there was a high prevalence of HBV infection among middle-aged groups and concluded that the most affected ages were the second, third, and fourth.

It is well known that protective immunity is not static but varies with age. Although there are distinct features of innate and adaptive immunity from fetal life to adulthood, which may alter the susceptibility of newborn infants to infections compared to adults, increased protection against certain infectious diseases during early life may benefit from a dampened immune response as a result of decreased immune pathology. This concept may offer an alternative interpretation of the different pathological manifestations clinically observed in HBV-infected patients during the natural history of infection.^[42]

There are very highly significant differences for people receiving the HBV vaccine through the current study [Table 3]. For example, some health personnel working

in the hospital laboratories found people vaccinated with HBV and became infected. However, they received the vaccine completely (three doses) and became infected after pricking a needle from an infected person. Therefore, people working in hospitals or centers for the digestive system and liver who are in direct contact with HBV patients need to be careful even after receiving three doses of the vaccine.

According to the questionnaire in this study, most of the unvaccinated people (75.9%) may be due to their lack of culture and low education, and they live in villages and unemployed. Moreover, Iraq's conditions involved embargoes and wars, especially after 2003, and subjected governorates to terrorism, adversely affecting vaccination campaigns and the nonarrival of health teams to some regions because of the wars, which led to the appearance of HBV in many Iraqi areas.

HBV vaccine has existed since 1982 and is given simultaneously with other generally administrated vaccines at birth and after a booster dose that remnants highly immunogenic. However, globally, the prevalence of the anti-HBsAg carrier state has altered rapidly since the availability and implementation of mass immunization in infants.^[43]

An important observation that can conclude from this study's results is that the emergence of such a situation in Iraq is contrary to what is expected. The vaccine may limit or restrict infection with the disease, so there is a possibility of the person receiving the immunization suffering from immunosuppression. Hence, the inability to produce an immune response or the method of administering the vaccine is incorrect (not well preserved), which has lost the efficiency of the vaccine, or the person suffers from a silent infection without clinical manifestation; this means that the affected person was in an incubation period, and consequently when the three doses were given, it triggered the action of the provirus.

A previous study indicated that the person is still infected if the anti-HBc is positive, suggesting that it is the source of antibodies from the infection and not from the vaccine. Therefore, this study's theoretical results confirm the virus reactivation in the body, which indicates a sudden increase in the proliferation of HBV.^[44]

The reactivation can happen spontaneously but is typically caused by cytotoxic chemotherapy or cancer immunosuppressive therapy, an autoimmune disease, or/and organ transplantation. It can be transient and clinically silent but often reasons a flare of disease that can be severe, subsequent in acute hepatic failure. Most cases of reactivation resolve spontaneously, but if immunosuppression is continued, the re-establishment of chronic hepatitis happens, leading to progressive liver injury and cirrhosis.^[44,45]

There are statistically significant differences in contact with the HBV through the current study, divided into three groups: house contact, work contact, and others. House contact was considered a risk group to infect with HBV because they have direct contact with infected patients, and the risk is increased when the infection is in the asymptomatic stage.^[46]

The result of the study found there were very highly significant differences between the two groups according to the disease status, which was recorded depending on the record of the infected persons ($P > 0.001$).

The acute case of HBV goes through four stages before beginning with the incubation period, approximately 12 weeks, and then moves to the stage for the onset of symptoms, which develop after the incubation period. First, high alanine aminotransferase (ATL) was observed, lasts 4–12 weeks, and includes anorexia, dark urine, jaundice, and right upper quadrant abdominal discomfort. Acute symptoms are uncommon in infants and children, but are common in adults. The third phase is a recovery period followed by the normalization of ATL levels. The last phase is the clearance of HBsAg in the serum, which follows after a few months of coinciding with the development of anti-HBs.^[47]

The chronic case starts in active and last for more than 6 months, and then moves to the chronic stage, which is the most common in humans and the leading cause of death among HBV,^[48] which is compatible with the results of our current study in the high incidence of chronic status between the HBV groups.

Clinicians may be concerned about whether HBV-related cirrhosis was associated with poor outcomes in COVID-19. The current study results showed highly significant differences between the two study groups regarding liver cirrhosis. It is worth noting that the present study showed the emergence of five sick cases infected with liver cirrhosis, which does not agree with the results of Xiang and Zheng,^[49] who showed significant differences and found only one case. Previous studies on the relationship between liver cirrhosis, HBV, and SARS-CoV-2 are very few or almost nonexistent at present, and these results do not agree with the findings of Zhang *et al.*^[50] on the impact of different hepatitis B status (HBV carrier group, hepatitis B/cirrhosis group) on COVID-19. Most HBV carriers do not develop a severe or critical illness, and no significant differences were found in the length of hospital stay, disease severity, and prognosis between the two groups.

In a large cohort study, Marjot *et al.*^[51] enrolled 745 CLD patients from 29 countries, of whom 386 had cirrhosis and 359 did not, and mortality was significantly higher in the cirrhotic patients (32% vs. 8%). Mortality increased with Child-Turcotte-Pugh class, which showed for the first time that the stage of liver disease is strongly associated with

COVID-19 mortality. The data from other multicenter retrospective studies also supported the conclusion that patients with liver cirrhosis in COVID-19 had higher mortality and worse prognoses than patients without cirrhosis.^[52] HBV-related cirrhosis only accounted for a small proportion of patients, and most cases of cirrhosis were attributed to nonalcoholic fatty liver disease (24%–32.5%), alcohol-related liver disease (4.6%–24%), and chronic hepatitis C virus infection (24%).^[53] More importantly, HBV accounted for the lowest proportion of severe cases and deaths compared with other etiologies. Alcohol-related liver disease rather than HBV was an independent risk factor associated with the outcome of COVID-19. Although the severity of cirrhosis is closely related to mortality and prognosis in COVID-19, the limited data about HBV-related cirrhosis are insufficient to confirm that HBV worsens the clinical outcome.^[49]

Most of the previous studies in the world on HBV reactivation were generally focused on and associated with cancer patients and their response to chemotherapy and immunosuppressive drugs, as well as biological therapy. However, the only case regarding HBV reactivation induced by COVID-19 was reported by Aldhaleei *et al.*^[30] from the United Arab Emirates. They reported that the patients with COVID-19 had an acute HBV infection and did not receive any immunosuppressive therapy.

In Iraq, there is no information available on the prevalence of HBV reactivation due to coinfection with other viral pathogens. In addition, there is no information regarding the incidence of HBV in SARS-CoV-2 patients. Therefore, this is the first study in Iraq about the incidence of HBV with SARS-CoV-2.

Liu *et al.*^[21] conducted a retrospective analysis of 21 patients with SARS-CoV-2 and HBV coinfection evaluated for HBV DNA viral load at least twice during hospitalization. Three of the 19 patients had HBV reactivation, characterized by an immediate increase in HBV DNA viral load from undetectable to high. Those individuals tested negative for hepatitis B envelop antigen and had not been treated with anti-HBV medication before admission. Two of the three patients were given methylprednisolone during their hospitalization, which could explain the reactivation, and one was given no corticosteroids at all. Another case report by Aldhaleei *et al.*^[30] revealed that one COVID-19 patient had acute HBV infection, with laboratory results showing AST (4933 U/L), ALT (4758 U/L), total bilirubin (183.9 mmol/L), HBsAg (+), hepatitis B core antibody immunoglobulin M (+), hepatitis B e antigen (–), and hepatitis B e antibody. There was no immunosuppressive therapy given to the patient. The patient could be at risk of HBV reactivation regardless of whether corticosteroids were given.

Following infection with SARS-CoV-2, the mechanisms of HBV reactivation are mostly due to a disrupted

equilibrium between the host's immune system and viral replication. Therefore, the intensity of glucocorticoids, immunosuppressive medications, and the host's baseline virological markers are primary risk factors for HBV reactivation after COVID-19 treatment.^[54,55] Although HBV reactivation is possible with SARS-CoV-2 infection, the overall risk is modest to low. In one prospective study,^[13] 61 patients with severe COVID-19-resolved HBV infection (HBsAg-negative, anti-hepatitis B core antibody-positive) following immunosuppressive medication were assessed for the likelihood of HBV reactivation. They discovered no HBsAg seroconversion instances after at least one follow-up, and just two (3%) patients had detectable serum HBV-DNA (15 IU/mL). Therefore, corticosteroids and immune suppressants can be prescribed therapeutically for patients with severe COVID-19 and coexisting HBV infection. Because of the danger of reactivation, the American Association for the Study of Liver Diseases strongly advises starting or continuing anti-HBV medication as soon as COVID-19 is detected.^[56-59] In addition, routine HBV virologic and liver-injury-related indicators should be closely followed.^[49]

CONCLUSIONS

We concluded that a high rate of HBV and SARS-CoV-2 coinfection was recorded in this study, especially among males. In addition, nonvaccinated cases of HBV alone or HBV with SARS-CoV-2 were predominated, whereas chronic HBV was more frequent than HBV alone or HBV with SARS-CoV-2. Regarding HBV reactivations, patients who had coinfection with SARS-CoV-2 have been recorded in acute and chronic cases of HBV patients, where no severe cases were recorded compared to the advanced cases of the disease who received immunosuppressive therapy and biological treatment. Therefore, it is necessary to consider the special care of persons exposed to infection with SARS-CoV-2 to patients infected with viral hepatitis, in particular, advanced cases of the disease and their stages of treatment as it leads to liver dysfunction and life-threatening complications.

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There are no conflicts of interest.

Author contributions

All authors contributed to conception and design, data analysis and interpretation, article writing, and final approval of the article.

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