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Original Article

Liver dysfunction and clinical outcomes of unvaccinated COVID-19 patients with and without chronic hepatitis B

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Abstract *Background:* Liver dysfunction is common during coronavirus disease 2019 (COVID-19), while its clinical impact and association with chronic hepatitis B (CHB) remain uncertain. We aimed to investigate liver dysfunction in COVID-19 patients and its impacts on those with/without CHB.
Methods: We conducted a retrospective cohort study of COVID-19 patients at National Taiwan University Hospital, stratified according to hepatitis B surface antigen (HBsAg) serostatus, with demographics, laboratory data, and hospitalization course reviewed, and clinical outcomes compared through multivariable analyses.
Results: We enrolled 109 COVID-19 patients unvaccinated against SARS-CoV-2 by August 2021. The HBsAg-positive group (n = 34) had significantly higher alanine aminotransferase (ALT) (26 vs. 16 U/L, P = 0.034), platelet (224 vs. 183 k/μL, P = 0.010) and longer hospitalizations (17 vs. 13 days, P = 0.012) compared with HBsAg-negative group (n = 75), while percentages of hepatitis (2-fold ALT elevation), oxygen supplementation, ventilators usage, COVID-specific treatment, intensive care unit (ICU) admission and mortality were comparable. Older age (odds

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ratio [OR]: 1.04, 95 % confidence interval [CI]: 1.00—1.08, P = 0.032) and higher aspartate aminotransferase (AST) (OR: 1.08, 95 % CI: 1.004—1.16, P = 0.038) were associated with oxygen supplementation according to multivariable analyses. Higher AST predicted ICU admission (OR: 1.11, 95 % CI: 1.03—1.19, P = 0.008). Oxygen usage (OR: 5.64, 95 % CI: 1.67—19.09, P = 0.005) and shock (OR: 5.12, 95 % CI: 1.14—22.91, P = 0.033) were associated with liver dysfunction.
Conclusions: CHB patients had higher ALT levels and longer hospitalizations during COVID-19. Higher AST levels predict severe COVID-19 and ICU admission.

Introduction

SARS-CoV-2, a novel coronavirus, was responsible for a cluster of pneumonia cases in Wuhan, China, at the end of 2019. It subsequently spread worldwide. By October 2023, Taiwan had recorded more than 10, 240, 000 confirmed SARS-CoV-2 cases, with 19,005 deaths. More than 696, 000, 000 people have been infected globally, with the number of deaths exceeding 6.92 million.

The SARS-CoV-2 disease, known as coronavirus disease 2019 (COVID-19), presents mainly as respiratory tract infection, with manifestations ranging from upper respiratory infection to pneumonia, acute respiratory distress syndrome, and even death. Liver dysfunction is one of the manifestations of COVID-19. Abnormal liver function tests (LFTs) are frequently observed (14%—53 %) among hospitalized, symptomatic COV ID-19 patients, with elevated serum aminotransferase levels and hyperbilirubinemia being most common.[1—6]

The pattern of abnormal LFTs among COVID-19 patients is generally hepatocellular.[7,8] Studies have proposed possible association between the severity of COVID-19 and liver dysfunction, with elevated serum aminotransferase levels more frequently observed in patients in intensive care units (ICUs) and in those requiring mechanical ventilation.[1,9,10] The impact of liver dysfunction on the COVID-19 course remains controversial. The effects of underlying chronic liver diseases, such as cirrhosis, CHB, and metabolic associated fatty liver disease (MAFLD), on the outcomes of COVID-19 have been investigated, but results are inconsistent. Some studies demonstrated lower critical illness and mortality rates among HBV carriers, some indicated no significant difference between HBV carriers and non-carriers, and other reported more severe hepatic dysfunction and metabolic disturbances among HBV carriers.[11—15] Moreover, treatment of COVID-19 was not standardized in these reports, which might affect the characteristics and outcomes of liver dysfunction. In this study, we investigated liver dysfunction, HBV status, and other factors associated with outcomes in COVID-19 patients.

Methods

Patients

COVID-19 patients were retrospectively reviewed, and their data were obtained from the electronic medical records of National Taiwan University Hospital (NTUH), a tertiary medical center in Taiwan. The diagnosis of COVID-19 was based on at least one positive RT-PCR (reverse transcription polymerase chain reaction) test for SARS-CoV-2 performed using a nasopharyngeal swab or sputum sample and analyzed using the Roche cobas 6800 or Abbott Alinity m system. Only those with documented HBsAg status were included in the study. Patients coinfected with chronic hepatitis C or incomplete medical data were excluded.

LFT results and relevant laboratory data were obtained upon admission and were measured biweekly, when necessary, during hospitalization. COVID-specific treatment mainly included corticosteroids, antiviral agent (remdesivir), and IL-6 (interleukin-6) antagonist (tocilizumab) administered according to the Clinical Management Guidelines issued by Taiwan Centers for Disease Control (CDC). Other supportive care was provided according to general clinical practices.

This study was approved by the Institutional Review Board of NTUH (202106105RIND) and conformed to the ethical principles for medical research involving human subjects of the 2013 version of the Declaration of Helsinki. The recruitment of informed consent for clinical trials was waived because of the retrospective nature of the study.

Data collection

Patients' electronic medical records were reviewed to obtain demographics, such as age, sex, body height, and weight, and underlying comorbidities regarded as risk factors for severe COVID-19. The Ct value of SARS-CoV-2 RT-PCR tests, baseline AST, ALT, peak ALT, platelet count, and total bilirubin were recorded, with a fibrosis-4 score calculated. The fibrosis-4 index, more commonly known as the FIB-4 index, was first proposed in 2006 by Sterling et al., which utilized indices including age, AST, ALT and platelet levels to predict liver fibrosis in patients with HIV/HCV coinfection. It was proven to be accurate in the prediction of hepatic fibrosis and reduced the need for liver biopsy in the majority of HIV/HCV coinfected patients.[16] In current clinical practice, the FIB-4 index is widely used to evaluate liver fibrosis not limited to HIV or HCV patients, and is regarded as a simple, easy-to-use and accurate tool which also serves as a "red-flag" for early identification of patients at high risk of advanced liver fibrosis and their referral to specialized care.[17] Specific treatment for COVID-19, clinical events during hospitalization and outcomes,

including development of shock, oxygen supplementation, mechanical ventilator usage, extracorporeal membrane oxygenation (ECMO), ICU admission, and death were recorded.

Endpoints

The primary endpoints of our study were comparison of liver dysfunction (abnormal ALT or total bilirubin), need for COVID-19-specific treatment (steroid, remdesivir, and tocilizumab administration), and COVID-19 severity (oxygen supplementation, development of shock, ICU admission, ventilator usage, ECMO, hospitalization length, and mortality) between patients with COVID-19 with and without CHB.

We also aimed to identify predictors of adverse outcomes of COVID-19, including inability to maintain adequate oxygenation status (SpO_2 >94 %) in ambient air requiring supplemental oxygen (defined as severe COVID-19), ICU admission, and death. Finally, we explored factors associated with liver dysfunction, which was defined as either abnormal total bilirubin or aminotransferase levels at the beginning or during hospitalization course.

Statistical analysis

Descriptive statistics are summarized using the median for continuous variables and are presented as proportions for the categorical data. Data were compared using Student's *t* test or the chi-square test to identify significant differences between the HBsAg-positive and HBsAg-negative groups. Univariate and multivariable Cox proportional hazards regressions and logistic regression analysis were performed. All statistical analyses were conducted using Stata (version 16; StataCorp, College Station, TX, USA). All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

A total of 461 patients were screened between March 5, 2020, and August 22, 2021, and 34 patients who were HBsAg positive were identified. We included another 75 age-matched and sex-matched patients who were HBsAg negative within the 461 screened patients for comparison. Finally, 109 patients with confirmed COVID-19 who were hospitalized at NTUH were included in the analysis. The median age was 59 years, and 46 % of the study sample were men. The age, sex, BMI (body mass index), SARS-CoV-2 RT-PCR Ct value, initial AST, and total bilirubin were comparable between the HBsAg positive and HBsAg-negative groups, and so were the risk factors for developing severe COVID-19, including obesity (defined as BMI >25 kg/m^2), underlying comorbidities such as cirrhosis, diabetes, renal failure, cardiovascular diseases, hypertension, and other conditions resulting in immunodeficient state (malignancy receiving anti-cancer therapy, human immunodeficiency virus infection, etc.), while the two groups also demonstrated similar rates of developing severe COVID-19. Meanwhile, the HBsAg-positive group had significantly higher baseline ALT levels (26 vs. 16 U/L, $P = 0.034$) and platelet counts (224 vs. 183 k/μL, $P = 0.010$) than the HBsAg-negative group (Table 1).

Outcomes of patients with COVID-19 with and without CHB

The HBsAg-positive group (n = 34) had significantly longer hospitalization periods (17 vs. 13 days, $P = 0.012$) than the HBsAg-negative group (n = 75). However, the percentage of hepatitis (>2-fold ALT elevation), oxygen supplementation,

Table 1 Baseline characteristics of COVID-19 patients by HBsAg positivity.

	HBsAg (−) N = 75	HBsAg (+) N = 34	P
Age, year	57 (28–90)	61 (40–80)	0.263
Male, n (%)	31 (41)	19 (56)	0.158
BMI	22.6 (17.4–37.6)	23.5 (19.1–30.5)	0.825
SARS-CoV-2 Ct value	22.6 (14.6–39.2)	23.9 (16.6–37.7)	0.283
AST, U/L	24 (14–309)	32 (14–883)	0.107
ALT, U/L	**16 (7–120)**	**26 (8–532)**	**0.034**
Total bilirubin, mg/dL	0.49 (0.21–1.4)	0.54 (0.25–8.3)	0.064
Platelet, K/uL	**183 (22–354)**	**224 (91–525)**	**0.010**
FIB-4 index	1.98 (0.58–21.03)	1.98 (0.31–11.06)	0.699
Severe COVID-19 (%)	41 (55)	21 (62)	0.488
Risk factors for severe COVID-19			
Obesity, n (%)	19 (25)	11 (32)	0.477
Cirrhosis, n (%)	1 (1)	1 (3)	0.562
Diabetes, n (%)	13 (17)	4 (12)	0.458
CKD, n (%)	2 (3)	1 (3)	0.935
CV disease, n (%)	7 (9)	2 (6)	0.544
Hypertension, n (%)	24 (32)	7 (21)	0.221
Others, n (%)	10 (13)	7 (21)	0.333

Data are expressed as median (range), or number (percentage).

ventilator usage, treatment with steroids, remdesivir, and tocilizumab, ICU admission, and mortality were comparable between the two groups (Table 2).

Among the 34 HBsAg-positive patients, none underwent anti-HBV therapy (nucleoside analogues [NUC]) before COVID-19, and eight (23.5 %) had liver dysfunction initially at the time of hospitalization for COVID-19, while 19 (55.8 %) had liver dysfunction throughout the COVID-19 course.

Effect of COVID-19-specific treatment

Because COVID-19-specific treatment may cause liver dysfunction, we investigated the impact of HBV coinfection in this scenario. Among the 75 HBsAg-negative patients, 32 received at least one of the COVID-19 standard treatments (remdesivir, tocilizumab, or dexamethasone) for severe disease, and 15 (15/32, 47 %) developed liver dysfunction after COVID-19-specific treatment. Among the 43 HBsAg-negative patients who did not receive any COVID-specific treatment, 13 (13/43, 30 %) developed liver dysfunction during COVID-19. Furthermore, 21 of 34 HBsAg-positive patients received COVID-19-specific treatment, eight (8/21, 38 %) developed liver dysfunction. Even 4 of the 9 (44 %) patients received NUC prophylaxis later developed liver dysfunction. Among the other 12 HBV carriers who received COVID-19-specific treatment without prophylactic NUC, four of them (33 %) later developed liver dysfunction. Moreover, 13 of the 34 HBsAg-positive patients did not receive any COVID-19-specific treatment, and six (6/13, 46 %) later developed liver dysfunction (Fig. 1 and Supplement Figure 1).

Effect of anti-HBV therapy

Throughout hospitalization, 10 HBsAg carriers were administered NUC. Among them, seven (70 %) were with normal liver function upon admission and were given NUC prophylactically, whereas three (30 %) were prescribed NUC because liver dysfunction was discovered upon admission. This liver dysfunction was presumed to be at least partly related to HBV, and, regardless of how mild the abnormalities were, NUC were prescribed to prevent further deterioration. Four of the 7 patients who received prophylactic NUC developed liver dysfunction during COVID, but with improved liver function documented prior to discharge, and the other 3 patients remained with normal liver function throughout hospitalization. On the other hand, among the 3 patients who received NUC due to liver dysfunction noted upon admission, normalized liver function was noted in 1 of them, while the other 2 patients had deteriorating liver dysfunction upon follow-up.

Five of the ten HBsAg-positive patients only received NUC during hospitalization and were lost to follow-up after discharge. Three other patients continued NUC after discharge for 6–12 months, and they had persistent HBV DNA suppression with normal liver function. The remaining two died during hospitalization because of COVID-19. Five HBsAg carriers with liver dysfunction at admission (baseline ALT ranging from 47 to 66 U/L and total bilirubin of 3.13 mg/dL) were never prescribed NUC, and all five had improved liver function later (Supplement Figure 2).

HBV reactivation

HBV DNA was tested in 26 HBsAg-positive patients during the COVID-19 course; among them, only six had baseline HBV DNA data prior to COVID-19 for comparison. Two HBsAg-positive patients experienced HBV reactivation (HBV DNA increases >100-fold) during COVID-19. Both received COVID-19 treatment during the course. One patient with previously undetectable HBV viral load was discovered to have HBV DNA 5900 IU/mL during admission, with an ALT up

Table 2 Outcomes of COVID-19 patients by HBsAg positivity.

Outcome	HBsAg (−) N = 75	HBsAg (+) N = 34	P
Liver function abnormalities			
Peak ALT, U/L	30 (7–341)	41 (10–1797)	0.101
Peak total-bilirubin, mg/dL	0.62 (0.25–32.55)	0.69 (0.29–14.77)	0.773
ALT elevation >2x upper limit of normal	11 (15)	5 (15)	0.996
COVID-specific treatment			
Steroid use, n (%)	27 (36)	18 (53)	0.096
Remdesivir use, n (%)	30 (40)	13 (38)	0.861
IL6RA use, n (%)	7 (9)	6 (18)	0.215
Adverse COVID-19 outcomes			
Oxygen use, n (%)	41 (55)	21 (62)	0.488
Shock, n (%)	9 (12)	8 (24)	0.124
ICU admission, n(%)	**14 (19)**	**12 (35)**	**0.059**
Ventilator use, n (%)	8 (11)	5 (15)	0.547
ECMO use, n (%)	2 (3)	1 (3)	0.935
Death, n (%)	3 (4)	3 (9)	0.306
Hospitalization days	**13 (4–75)**	**17 (2–167)**	**0.012**

Data are expressed as number (percentage); Peak refers to the highest value documented during the hospitalization course; IL6RA: interleukin-6 receptor antagonist, e.g. tocilizumab; oxygen use refers to inability to maintain SpO2 >94 % under ambient air requiring supplemental oxygen use; shock refers to the requirement of vasopressor/inotropic agent use.

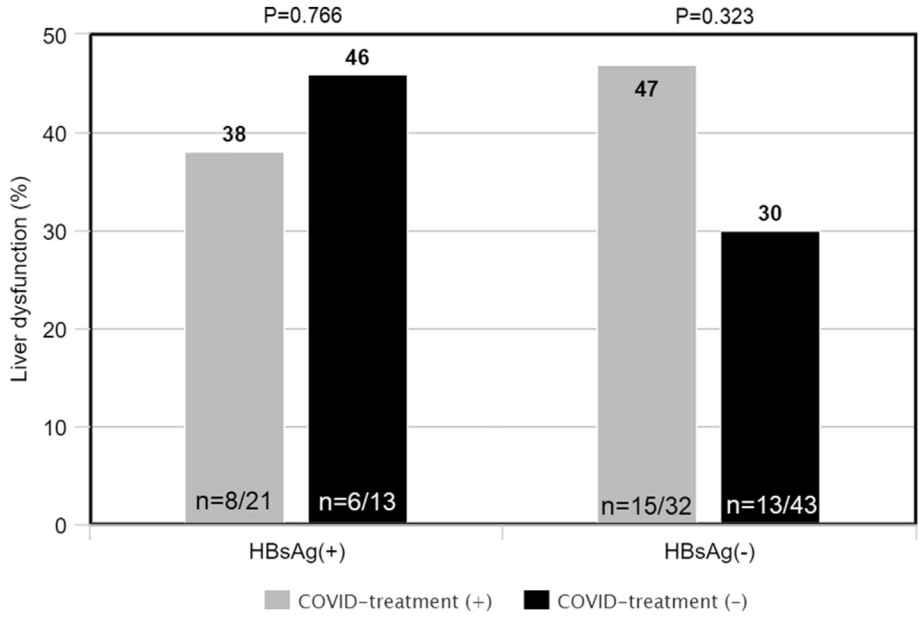

Figure 1. Percentage of liver dysfunction among HBsAg carriers and non-carriers with and without COVID-specific treatment.

to 59 U/L. Entecavir was administered, and follow-up HBV DNA and ALT levels normalized thereafter.

The other patient exhibited increased HBV DNA from 518 to 54800 IU/mL with concurrent liver dysfunction (ALT of 89 U/L and total bilirubin of 4.25 mg/dL) during COVID-19. Entecavir was prescribed, but this patient eventually died from severe COVID-19.

Predictors for adverse outcomes of COVID-19

Baseline characteristics including age, sex, BMI, as well as baseline SARS-CoV-2 RT-PCR Ct value, HBsAg status, AST, ALT, platelet count, and FIB-4 index were evaluated to explore possible predictors of adverse outcomes of COVID-19, which included severe COVID-19, ICU admission, and death.

Univariate analysis revealed that older age (odds ratio [OR]: 1.06, 95 % confidence interval [CI]: 1.02—1.10, P = 0.002), higher AST (OR: 1.06, 95 % CI: 1.02—1.10, P = 0.006), and higher ALT (OR: 1.04, 95 % CI: 1.00—1.07, P = 0.046) were associated with severe COVID-19. Further multivariable analysis revealed that only older age (OR: 1.04, 95 % CI: 1.00—1.08, P = 0.032) and higher AST (OR: 1.08, 95 % CI: 1.004—1.16, P = 0.038) were associated with severe COVID-19 (Table 3).

Regarding ICU admission, both univariate and multivariable analyses revealed that only higher baseline AST was predictive of ICU admission (OR: 1.11, 95 % CI: 1.03—1.19, P = 0.008; Table 4).

As for mortality, according to Cox proportional hazards regression analysis, none of the analyzed factors was predictive of the outcome of death (Supplement Table 1).

Factors associated with liver dysfunction during COVID-19

Together with the aforementioned factors, we evaluated the association of COVID-19-specific treatment with liver dysfunction considering the complex mechanisms of hepatotoxicity. Among all the studied factors, multivariable analysis indicated that oxygen supplementation (OR: 5.64, 95 % CI: 1.67—19.09, P = 0.005) and development of shock (OR: 5.12, 95 % CI: 1.14—22.91, P = 0.033) were associated with liver dysfunction (Table 5).

Table 3 Predictors for requirement of oxygen use in COVID-19 patients.

	OR (95%CI)	P	Adjusted OR (95%CI)	P
Age (per 1 year increase)	1.06 (1.02—1.10)	0.002	1.04 (1.00—1.08)	0.032
Male (vs. female)	2.01 (0.92—4.37)	0.078	1.43 (0.59—3.47)	0.427
BMI (per 1 kg/m2 increase)	1.11 (0.98—1.25)	0.094		
SARS-CoV-2 Ct (per 1 unit increase)	1.01 (0.94—1.09)	0.762		
HBsAg (vs. negative)	1.34 (0.59—3.07)	0.489		
AST (per 1 U/L increase)	**1.06 (1.02—1.10)**	**0.006**	**1.08 (1.004—1.16)**	**0.038**
ALT (per 1 U/L increase)	1.04 (1.00—1.07)	0.046	0.97 (0.90—1.04)	0.373
Platelet (per 1 k/μL increase)	1.00 (0.99—1.00)	0.484		
FIB-4 (per 1 unit increase)	1.21 (0.96—1.52)	0.102		

Table 4 Predictors for ICU admission in COVID-19 patients.

	OR (95%CI)	P	Adjusted OR (95%CI)	P
Age (per 1-year increase)	1.05 (1.01—1.09)	0.021	1.03 (0.97—1.08)	0.337
Male (vs. female)	3.59 (1.40—9.21)	0.008	1.80 (0.56—5.78)	0.324
BMI (per 1 kg/m2 increase)	1.07 (0.95—1.22)	0.270		
SARS-CoV-2 Ct (per 1 unit increase)	0.97 (0.88—1.06)	0.492		
HBsAg (vs. negative)	2.38 (0.95—5.92)	0.063	2.23 (0.68—7.29)	0.185
AST (per 1 U/L increase)	**1.06 (1.03—1.10)**	**<0.001**	**1.11 (1.03—1.19)**	**0.008**
ALT (per 1 U/L increase)	1.05 (1.01—1.08)	0.007	0.93 (0.86—1.02)	0.122
Total-bilirubin (per 1 mg/dL increase)	3.19 (0.94—10.77)	0.062	0.97 (0.25—3.81)	0.970
Platelet (per 1 k/μL increase)	1.00 (0.99—1.00)	0.566		

Discussion

The present study revealed no significant difference in adverse outcomes of COVID-19 in patients with or without CHB, except for prolonged hospitalization of HBV carriers. Baseline AST levels were significantly associated with adverse outcomes of developing severe COVID-19, requiring oxygen supplementation and ICU admission, but no specific factor was associated with mortality. In turn, developing shock and desaturation requiring supplemental oxygen are two critical factors significantly related to liver dysfunction.

COVID-19 and liver dysfunction

Liver dysfunction, which is mainly characterized by elevated serum aminotransferase levels, is often observed in patients with COVID-19. According to a multicenter retrospective cohort study of 5771 adult COVID-19 pneumonia patients in Hubei Province conducted by Lei et al., liver injury dynamic patterns differ in terms of ALT, AST, ALP, and total bilirubin: AST elevated first, followed by ALT, whereas fluctuations in bilirubin levels remained mild; AST abnormality was associated with the highest mortality risk compared with other indicators of liver injury.[18] The results of our study are in line with those of the aforementioned study, indicating that higher AST levels were predictive of the development of severe COVID-19 and ICU admission. Hyperbilirubinemia detected in our patients was also generally mild; 18 of the 24 patients (75 %) who developed hyperbilirubinemia during COVID-19 had serum total bilirubin of only 1—3 mg/dL.

Cause of liver dysfunction during COVID-19

The pathogenesis of liver dysfunction is considered to be either direct cytotoxicity or immune-mediated liver injury, with immune-mediated liver injury being the more widely accepted mechanism.[19] In SARS-CoV-2 infection, both innate and acquired immune systems elicit antiviral responses. Pathogen-associated molecular patterns and specific viral antigens are identified, and cytokines and chemokines are released, subsequently activating macrophages and T cells to eradicate virus and virus-infected cells.[20] As verified in multiple studies, increased inflammatory cytokine release was observed in COVID-19

Table 5 Factors associated with liver dysfunction (n = 45) in COVID-19 patients at or during admission.

	OR (95%CI)	P	Adjusted OR (95%CI)	P
Baseline characteristics				
Age (per 1-year increase)	1.00 (0.97—1.03)	0.962	0.96 (0.92—1.00)	0.054
Male (vs. female)	1.67 (0.77—3.61)	0.191	1.19 (0.47—3.01)	0.716
BMI (per 1 kg/m2 increase)	1.01 (0.91—1.13)	0.818		
SARS-CoV-2 Ct (per 1 unit increase)	1.00 (0.93—1.08)	0.944		
HBsAg (vs. negative)	1.68 (0.74—3.81)	0.215	1.46 (0.54—3.94)	0.459
Platelet (per 1 k/μL increase)	1.00 (1.00—1.01)	0.899		
FIB-4 (per 1 unit increase)	1.09 (0.93—1.28)	0.266		
COVID-specific treatment				
Remdesivir (vs. no use)	2.71 (1.22—5.99)	0.014	0.96 (0.28—3.23)	0.943
Steroid (vs. no use)	3.24 (1.46—7.20)	0.004	0.91 (0.28—2.94)	0.873
IL6RA (vs. no use)	3.75 (1.08—13.06)	0.038	1.43 (0.33—6.13)	0.632
Adverse COVID-19 outcomes				
Oxygen use (vs. no use)	**5.85 (2.41—14.16)**	**<0.001**	**5.64 (1.67—19.09)**	**0.005**
Shock (vs. no shock)	**9.18 (2.45—34.37)**	**0.001**	**5.12 (1.14—22.91)**	**0.033**

Liver dysfunction is defined as either abnormal total bilirubin or aminotransferase levels at or during the hospitalization course; IL6RA: interleukin-6 receptor antagonist, e.g. tocilizumab; oxygen use refers to inability to maintain SpO2 >94 % under ambient air requiring supplemental oxygen use; shock refers to the requirement of vasopressor/inotropic agent use.

patients.[21,22] The aforementioned cascade of events eventually leads to liver damage. Moreover, to further complicate the process, COVID-19 patients, especially those with severe COVID-19, often experience altered hemodynamics, oxygenation status, and fluid overload resulting in liver congestion, which may also contribute to liver dysfunction. Drug-induced liver injury,[3] as well as reactivation of HBV resulting from immunosuppressive agents, including corticosteroids and IL-6 antagonists, are also potential concerns.

In our study, among the 109 included patients, 53 received COVID-19-specific treatment, among whom 23 (43.3 %) had normal liver function at admission but later developed liver dysfunction. Whether the causes of liver dysfunction are attributable to severe COVID-19 or to hepatotoxicity induced by COVID-19-specific treatment cannot be thoroughly clarified. Nevertheless, our results suggest that the liver function of those receiving COVID-19-specific treatment must be monitored regardless of their comorbidities.

We observed that the need for oxygen supplementation and development of shock were associated with liver dysfunction. It is because oxygenation and hemodynamic status are significantly disturbed during severe COVID-19, both of which are predominantly related to systemic inflammation triggered by SARS-CoV-2 and are likely to cause further liver damage through other mechanisms, such as liver ischemia, liver congestion, and tissue hypoxemia. This is probably the reason why AST, although being less specific for liver injury as compared with other liver function indices such as ALT, is most significantly related to the degree of COVID-19 severity, since its elevation could be due to damage of other organ systems and systemic inflammation, as in the case of severe SARS-CoV-2 infection with collateral liver damage. We were unable to trace the exact events of every liver function fluctuation during the COVID-19 course because of each patient's unique, complex clinical course and were unable to clarify the time sequence because of the retrospective nature of the current research. In summary, close monitoring of liver function throughout the whole COVID-19 course, especially in those with severe COVID-19, is warranted, which is also recommended by the updated guidelines from the American Association for the Study of Liver Diseases (AASLD; October 2022).[23,24]

HBV and COVID-19

Several studies have reported the various effects of HBV during COVID-19. According to the coronavirus disease 2019-hepatitis B virus-Chinese Portal Hypertension Diagnosis and Monitoring Study Group, which consecutively monitored COVID-19 patients in 10 designated hospitals in China, those with preexisting HBV infection had lower incidence of ICU admission and mortality rate.[13] This finding may be related to host immune responses in the interplay between HBV and SARS-CoV-2, but the results could not be fully validated because of the study's small sample of patients with preexisting CHB (15 among the total 571 patients, which is lower than the incidence of HBV infection in the overall Chinese population [5.7 %]).

In another retrospective study of 326 COVID-19 patients, 20 (6.1 %) were with HBV coinfection. No significant differences in the rate of liver dysfunction, rate of discharge, or length of hospitalization were found between patients with and without HBV infection.[14] Liu et al. studied 50 patients coinfected with SARS-CoV-2 and HBV, 56 infected with SARS-CoV-2 only, 57 with HBeAg-negative CHB, and 57 healthy controls, and revealed that SARS-CoV-2 and HBV coinfection did not significantly affect the COVID-19 outcomes in terms of mortality, recovery, and hospitalization length. However, HBV carriers had more severe monocytopenia, thrombocytopenia, hypoalbuminemia, and dyslipidemia than HBsAg negative patients.[15] Yip et al. conducted a territory-wide retrospective cohort study in Hong Kong between 2020 and 2021 involving 5639 patients, among which 353 (6 %) and 359 (6.4 %) had current and past HBV infection, respectively. Neither current nor past HBV infection was found to be associated with increased liver injury (defined as ALT or AST >2 times the upper limit of normal with total bilirubin of ≥ 2.2 mg/dL or international normalized ratio of ≥ 1.7) or mortality.[25]

In the present study, compared with HBsAg-negative patients, CHB patients had higher baseline ALT levels and longer hospitalization lengths; however, their clinical outcomes were comparable. Possible explanation for the inconsistency between our results and those of the aforementioned studies involves the heterogeneous, nonunified treatment for COVID-19 during the initial worldwide SARS-CoV-2 outbreaks and the different sample sizes in different studies. The patients in our study contracted SARS-CoV-2 predominantly between May and July 2021, when the delta strain was dominant; compared with other prior strains, the delta strain causes milder and shorter symptoms but is more transmissible.[26]

We observed that liver dysfunction developed among 70 % ($n = 7$) of the CHB patients with COVID-19, even after they received NUC during hospitalization, which indicates the critical role of other contributing factors to liver dysfunction.

HBV reactivation rates among patients with COVID-19 and HBV coinfection remains unclear. The 2022 AASLD guidelines and the 2020 Asian Pacific Association for the Study of the Liver expert panel suggest that NUC treatment can be given to HBV carriers with COVID-19 prophylactically before IL-6 antagonist or other immunosuppressive therapy, particularly with suspicion of hepatitis B flare.[27] Our study verified two cases of HBV reactivation, and because liver dysfunction is common during COVID-19, NUC prophylaxis may minimize liver dysfunction induced by HBV reactivation.

Strengths and limitations

Our study demonstrated the frequency of liver dysfunction in patients infected with SARS-CoV2 and the clinical consequences of liver dysfunction in patients receiving evidence-based COVID-19-specific treatments according to established CDC guidelines at that time. Searching into current literature, studies focusing solely on the delta variant are yet limited. Our studied COVID-19 patients were enrolled between March 5, 2020, and August 22, 2021.

During this period, the predominant SARS-CoV-2 variant worldwide and in Taiwan was the delta strain. COVID vaccination was not yet widely available then in Taiwan, and there are very limited infected patients according to the strict quarantine policy in Taiwan. Now, the omicron strain has replaced the delta strain to become the most prevalent viral strain, while it possesses reduced transmissibility and has lower incidence of liver dysfunction.[28] Increasing vaccination coverage against COVID-19 worldwide also lowered the critical illness rates of COVID-19 as well as the rates of associated liver dysfunction. Meanwhile, since the COVID-19 severity was significantly higher during our studied delta variant pandemic, our study results better reflect the natural SARS-CoV-2 disease course and actual impact of COVID-19 on liver function and viral hepatitis B status, especially from the most virulent delta strain, without the interference of vaccinations or specific antiviral agents, and thus it helps to understand more about the pathogenesis of COVID-19. Therefore, even during the present omicron era, in current clinical practice, our study results may be applied to the care of immunocompromised COVID-19 patients who shared clinical circumstances similar to our studied patients.

There are still limitations in our current study. Our HBV DNA data were incomplete for all the CHB patients; therefore, we cannot confirm every HBV reactivation event, and our cohort can only provide information on liver dysfunction during hospitalization. Meanwhile, our enrolled COVID-19 patients were mostly unable to receive abdominal ultrasound or elective image studies because of strict isolation policies at that time, and thus the status of cirrhosis could not be fully investigated in every patient. We thus used alternative, objective value, mainly the FIB-4 index, to evaluate their baseline liver reserve.

In conclusion, our results revealed that CHB patients with COVID-19 have higher ALT and longer hospitalization than patients without HBV. Higher AST are predictive of severe COVID-19 and ICU admission. We recommend liver function monitoring in COVID-19 patients.

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Ethics approval

This study was approved by the Institutional Review Board of National Taiwan University Hospital (202106105RIND) and conformed to the ethical principles for medical research involving human subjects of the Declaration of Helsinki updated in 2013. The informed consent was waived because this is a retrospective study conducted by a review of medical records only.

Author contributions

Hao-Che Chang: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript.
Tung-Hung Su: study concept and design; acquisition of data; statistical analysis and interpretation of data; drafting of the manuscript; obtained funding; study supervision.
Yu-Tsung Huang: acquisition of data and interpretation of data.
Chun-Ming Hong: acquisition of data and interpretation of data.
Wang-Huei Sheng: acquisition of data and interpretation of data.
Po-Ren Hsueh: study concept and design; critical review of manuscript.
Jia-Horng Kao: study concept and design; interpretation of data; study supervision, critical review of manuscript.

Declaration of competing interest

T.-H. S. received research grant from Gilead Sciences, and was on speaker's bureaus for Abbvie, Bayer, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, and Takeda.
J.-H. K. has served as a consultant for Abbvie, Abbott, Gilead Sciences, Roche, and Sysmex and on speaker's bureaus for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, and Sysmex.
Others declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.11.003.