A case series of COVID-19 patients with chronic hepatitis B virus infection

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Abstract
Previous studies reported that coronavirus disease 2019 (COVID-19) was likely to result in liver injury. However, few studies reported the impacts of COVID-19 on liver function in patients with chronic liver diseases. We aimed to describe a case series of COVID-19 patients with chronic hepatitis B virus (HBV) infection. Confirmed hospitalized COVID-19 patients from hospitals in 10 cities of Jiangsu province, China, were retrospectively included between 18 January 2020 and 26 February 2020. Demographic information, epidemiologic data, clinical features, and treatment data were extracted from medical records. Seven COVID-19 patients with chronic HBV infection were included. Six (85.7%) patients were male. The patients aged from 33 to 49 years. Two patients had HBV-related cirrhosis. One patient (14.3%) was positive for serum HBV e-antigen. On admission, 1 (14.3%) patient had mildly elevated alanine aminotransferase (ALT) level (>40 U/L) and 1 (14.3%) had elevated aspartate aminotransferase (AST) level (>40 U/L). The serum albumin level and platelet counts were decreased in two patients with HBV-related liver cirrhosis. Three (42.9%) patients had elevated ALT level and 2 (28.6%) patients had elevated AST level in hospitalization. However, the peak ALT and AST level during hospitalization was 51 U/L and 44 U/L, respectively. As of 29 February 2020, all patients were discharged. No patient was admitted to the intensive care units or

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; COVID-19, coronavirus disease 2019; CT, computed tomography; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; ICU, intensive care units; Tbil, total bilirubin; WHO, World Health Organization.

Yang Li, Chunyang Li, and Jian Wang contributed equally.
developed liver failure during hospitalization. The abnormalities of liver function are not uncommon on COVID-19 patients with chronic HBV infection in our case series. However, no patient developed severe liver-related complications during hospitalization.

KEYWORDS
chronic hepatitis B, clinical features, coronavirus disease 2019

1 | INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) outbreak in Wuhan and spread rapidly all over the world. As of 12 June 2020, 7,410,510 confirmed cases and 418,294 deaths have been reported. The overall case-fatality rate was reported to be 2.3% according to a report from the Chinese center for disease control and prevention. The clinical characteristics of COVID-19 patients have been described in several studies. Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, the impairment of other organs are demonstrated.

Previous studies reported that COVID-19 was likely to induce liver injury as serum levels of alanine aminotransferase (ALT) were increased in 28% and aspartate aminotransferase (AST) were increased in 35% of patients, particularly in those who were admitted to the intensive care units (ICU). Guan et al summarized the clinical characteristics of 1099 patients with confirmed COVID-19 from 552 hospitals in 30 provinces of China. The rates of ALT more than 40 U/L and AST more than 40 U/L were 22.2% and 21.3%, respectively. 10.5% of the COVID-19 patients had elevated serum total bilirubin (Tbil).

However, to the best of our knowledge, few studies have reported the impacts of COVID-19 on liver function in patients with chronic liver diseases such as chronic hepatitis B (CHB). We described a case series of confirmed COVID-19 patients with chronic hepatitis B virus (HBV) infection.

2 | METHODS

2.1 | Population

Three hundred and forty-two confirmed COVID-19 patients hospitalized in hospitals in 10 cities of Jiangsu province (Suzhou, Huaian, Changzhou, Xuzhou, Taizhou, Yangzhou, Nantong, Suqian, Yancheng, Lianyungang), China between 18 January 2020 and 26 February 2020 were retrospectively included. One hundred and forty (40.9%) patients were excluded due to the negativity of serum hepatitis B surface antigen during hospitalization. The remaining 195 patients were not tested for HBV markers. However, among the 195 patients, 191 patients had no medical history of chronic HBV infection and four patients having a medical history of chronic HBV infection but without serum HBV test results during hospitalization were also excluded. Eventually, seven COVID-19 patients coinfected HBV were enrolled in our study (Figure 1). The COVID-19 patients were diagnosed based on the
criterion of the World Health Organization’s interim guidance.\textsuperscript{9} Chronic HBV infection was defined as a known medical history of positive for serum HBV surface antigen (HBsAg) for more than 6 months. Patients were excluded from this study for the following reasons: coinfection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus (HIV), combined with a primary biliary cirrhosis, autoimmune hepatitis, alcoholic hepatitis or nonalcoholic fatty hepatitis. The criteria for discharge was according to the guidelines for the diagnosis and treatment of novel coronavirus infection by the Chinese National Health Commission (Trial Version 6).\textsuperscript{9} We randomly selected 21 COVID-19 patients without chronic HBV infection as controls by age and gender matching with chronic HBV infected patients with the ratio of 3:1.

This study was approved by the institutional review boards of hospitals. Informed consent was waived due to a public health outbreak investigation.

2.2 | Procedures

Medical records of all confirmed COVID-19 patients who were hospitalized were reviewed by more than two health care workers in each medical center. Demographic information, epidemiologic data, clinical features, and treatment data were extracted from medical records. Data were recorded into a computerized database and cross-checked by different researchers to avoid errors.

2.3 | Laboratory and radiologic information

Throat swabs were tested for COVID-19 by real-time polymerase chain reaction according to the recommended protocol.\textsuperscript{10} The laboratory tests included blood routine tests, liver function, coagulation function, inflammatory biomarkers, HBV markers, and HBV DNA levels. Chest computed tomography (CT) or chest radiographs were performed for each patient and the results were collected.

2.4 | Statistical analysis

The continuous variables were presented as medians (interquartile range). Categorical variables were shown as the counts and percentages. The independent group t tests or Mann-Whitney U were used to compared continuous variables between groups. The χ² or Fisher exact test was used for the comparisons of categorical variables. \( P < .05 \) was considered statistically significant. All data analysis was performed using SPSS version 22.0 software (SPSS Inc, Chicago, IL).

3 | RESULTS

3.1 | Demographic and epidemiologic characteristics

The demographic and epidemiologic characteristics of the patients are presented in Table 1. Six (85.7%) patients were male. The patients aged from 33 to 49 years. Four patients had known contact with confirmed COVID-19 cases and one patient visited Wuhan 2 weeks before the diagnosis. All patients had a medical history of chronic HBV infection. Two patients had HBV-related cirrhosis. No patients had chronic hepatitis C, nonalcoholic fatty liver disease, or hepatocellular carcinoma. Two patients received anti-HBV treatment with entecavir for 3 and 7 years, respectively.

3.2 | Clinical features and laboratory abnormalities

All patients presented fever and 5 (71.4%) patients had cough at onset of illness (Table 2). Two patients had shortness of breath and one patient had fatigue. A total of 2 (28.5%) patients showed lymphopenia on admission. Two patients had elevated serum C-reactive protein (>10 mg/L).

TABLE 1  Demographic and epidemiologic characteristics of seven confirmed COVID-19 patients with chronic HBV infection

| Characteristics                                      | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|------------------------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Age, y                                               | 47        | 49        | 49        | 41        | 33        | 34        | 49        |
| Sex                                                  | Male      | Male      | Male      | Male      | Male      | Male      | Female    |
| Underlying chronic liver diseases                    |           |           |           |           |           |           |           |
| Chronic hepatitis B                                  | Yes       | Yes       | Yes       | Yes       | Yes       | Yes       | Yes       |
| Chronic hepatitis C                                  | No        | No        | No        | No        | No        | No        | No        |
| Hepatocellular carcinoma                            | No        | No        | No        | No        | No        | No        | No        |
| Cirrhosis                                            | No        | No        | Yes       | No        | No        | No        | No        |
| Nonalcoholic fatty liver disease                     | No        | No        | No        | No        | No        | No        | No        |
| Autoimmune liver diseases                            | No        | No        | No        | No        | No        | No        | No        |
| Exposure history                                     |           |           |           |           |           |           |           |
| Contact with confirmed patients                      | No        | No        | No        | Yes       | Yes       | Yes       | Yes       |
| Visited Wuhan                                        | No        | Yes       | No        | No        | No        | No        | No        |
| Unknown                                              | Yes       | No        | Yes       | No        | No        | No        | No        |

Abbreviations: COVID-19, coronavirus disease 2019; HBV, hepatitis B virus.
All patients were positive for serum HBsAg on admission. Only 1 (14.3%) patient was positive for serum HBV e-antigen. On admission, 1 (14.3%) patient had mildly elevated ALT level (>40 U/L) and 1 (14.3%) had elevated AST level (>40 U/L). The serum albumin level and platelet counts were decreased in two patients with HBV-related liver cirrhosis. Only one patient had elevated serum total bilirubin on admission. Serum HBV DNA loads were tested in two patients and both had undetectable serum HBV DNA (<20 IU/mL).

The dynamic changes of ALT, AST, and Tbil are presented in Figure 2. A total of 3 (42.9%) patients had elevated ALT level and 2 (28.6%) patients had elevated AST level during hospitalization. Four patients (57.1%) had elevated serum Tbil (>17.1 μmol/L) during hospitalization. However, the peak ALT, AST, and Tbil during hospitalization were 51 U/L, 44 U/L, and 36.2 μmol/L, respectively. All patients had abnormalities of chest CT images. Five of the patients had ground-glass opacity on chest CT images.

### 3.3 Complications, treatment, and outcomes

Oxygen therapy was administered in four patients (Table 3). However, no patient received mechanical ventilation. All patients were treated with antiviral drugs (lopinavir/ritonavir [five cases]; atomized inhalation of interferon α-2b [four cases]; arbidol [five cases]; oseltamivir [one case]). All patients were administered with empirical antibiotic treatment. Two patients were given corticosteroids and one patient was given gamma globulin. As of 29 February 2020, all patients were discharged. The duration of hospitalization ranged from 12.0 to 20.0 days. No patient was admitted to the ICU or had any severe complications including liver failure during hospitalization.

| Characteristics                  | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Onset symptoms and signs         |           |           |           |           |           |           |           |
| Fever                            | Yes       | Yes       | Yes       | Yes       | Yes       | Yes       | Yes       |
| Cough                            | Yes       | No        | No        | Yes       | Yes       | Yes       | Yes       |
| Shortness of breath              | No        | No        | No        | Yes       | No        | No        | Yes       |
| Sore throat                      | No        | No        | No        | No        | No        | No        | No        |
| Fatigue                          | No        | No        | No        | Yes       | No        | No        | No        |
| Muscle ache                      | No        | No        | No        | No        | No        | No        | No        |
| Laboratory tests                 |           |           |           |           |           |           |           |
| White blood cells (×10^9/L)      | 2.05      | 5.21      | 4.12      | 5.92      | 5.94      | 4.50      | 4.90      |
| Decreased                        | Yes       | No        | No        | No        | No        | No        | No        |
| Lymphocyte (10^9/L)              | 0.55      | 1.94      | 0.91      | 1.26      | 1.71      | 1.60      | 0.90      |
| Decreased                        | Yes       | No        | No        | No        | No        | No        | Yes       |
| Platelet (10^9/L)                | 96        | 210       | 74        | 150       | 166       | 213       | 140       |
| Decreased                        | Yes       | No        | Yes       | No        | No        | No        | No        |
| PCT, ng/mL                       | 0.039     | 0.025     | NA        | 0.071     | <0.1      | 0.03      | 0.08      |
| CRP, mg/L                        | 18        | 4.74      | NA        | 2.1       | 5.2       | 0         | 10.4      |
| ALT, U/L                         | 29        | 31        | 30        | 31        | 17        | 45        | 38        |
| Peak ALT during hospitalization  | 42        | 31        | 30        | 51        | 31        | 45        | 38        |
| AST, U/L                         | 31        | 27        | 41        | 34        | 21        | 30        | 31        |
| Peak AST during hospitalization  | 44        | 27        | 41        | 34        | 25        | 30        | 31        |
| Tbil, μmol/L                     | 12.0      | 2.9       | 11.1      | 16.6      | 13.9      | 27.6      | 12.7      |
| Peak Tbil during hospitalization | 36.2      | 17.2      | 11.1      | 16.6      | 13.9      | 27.6      | 19.3      |
| Albumin, g/L                     | 32.2      | 44.4      | 35.3      | 40.5      | 44.7      | 46.7      | 43.4      |
| PT, s                            | 12.1      | 13        | 13.7      | 13.2      | 13.9      | 13.1      | 12.9      |
| HBsAg                            | Positive  | Positive  | Positive  | Positive  | Positive  | Positive  | Positive  |
| HBeAg                            | Negative  | Negative  | Negative  | Negative  | Positive  | Negative  | Negative  |
| HBV DNA, IU/mL                   | NA        | NA        | NA        | NA        | NA        | <20       | <20       |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; HBV, hepatitis B virus; HBeAg, hepatitis B virus e-antigen; HBsAg, hepatitis B virus surface antigen; Tbil, total bilirubin; PT, prothrombin time; NA, not available.
3.4 Comparisons of clinical characteristics between COVID-19 patients with and without chronic HBV infection

We further compared the clinical features of COVID-19 patients with and without chronic HBV infection. The results revealed that the symptoms, laboratory tests, chest CT, hospitalization days, and ICU admission rate were similar between these two groups. The levels of prothrombin time (PT) were higher in chronic HBV infected patients than non-HBV patients. However, the median levels of PT in these two groups were within the normal range (Table 4).

4 DISCUSSION

A case series of seven CHB patients with COVID-19 were included from five hospitals in Jiangsu province, China. This study showed that only one patient had elevated ALT and one patient had elevated AST on admission. However, 3 (42.9%) patients developed mild elevated ALT levels and 2 (28.6%) patients had mild elevated AST levels during hospitalization. Furthermore, during hospitalization, four patients developed elevated Tbil. The rate of abnormalities of ALT and Tbil seems to be higher than the general population as previously reported. However, the elevated levels of ALT and Tbil were generally not high (<2 × ULN) in our study, indicating the COVID-19-related liver injury was not severe even for patients with chronic HBV infection. Tian et al also demonstrated that liver pathology only showed mild sinusoidal dilatation in COVID-19 patients. Although we could not fully exclude the possibility that the abnormalities of ALT and Tbil might be induced by HBV, two patients with HBV DNA less than 20 IU/mL had elevated ALT and Tbil during hospitalization suggesting that the abnormalities might be more likely induced by COVID-19.

TABLE 3 Treatment and outcomes of seven confirmed COVID-19 patients with chronic HBV infection

| Characteristics                  | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Treatment                        | Oxygen therapy | Yes | No | No | Yes | Yes | No | Yes |
|                                  | Mechanical ventilation | No | No | No | No | No | No | No |
| Antiviral therapy for COVID-19   | Lopinavir/ritonavir | Yes | Yes | No | Yes | No | Yes | Yes |
|                                  | Interferon α-2b    | No | Yes | Yes | Yes | No | No | Yes |
|                                  | Arbidol           | Yes | No | No | Yes | Yes | Yes | Yes |
|                                  | Oseltamivir       | No | No | Yes | No | No | No | No |
|                                  | Antibiotic therapy| Yes | Yes | Yes | Yes | Yes | Yes | Yes |
|                                  | Gamma globulin    | No | No | No | No | No | No | No |
|                                  | Corticosteroid    | No | No | No | Yes | No | No | Yes |
|                                  | Antiviral treatment for HBV | Yes | No | No | No | Yes | No | No |
|                                  | Antiviral HBV drug| Entecavir | No | No | No | Entecavir | No | No |
| Outcomes                         | Hospital discharge | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
|                                  | Hospital stay, d   | 20 | 17 | 13 | 15 | 17 | 17 | 12 |
|                                  | ICU admission      | No | No | No | No | No | No | No |
|                                  | Liver failure      | No | No | No | No | No | No | No |

Abbreviations: COVID-19, coronavirus disease 2019; HBV, hepatitis B virus; ICU, intensive care unit.
In addition, all patients in the present study received antiviral treatment for COVID-19. Lopinavir/ritonavir, atomized inhalation of interferon α-2b, and arbidol are recommended antivirus regimens in diagnosis and treatment of COVID-19 issued by National Health Commission of China and widely used for the treatment of COVID-19.\(^9\) Lopinavir/ritonavir is a drug used in combination with other medicines for the treatment of adults and children who are infected with HIV.\(^12,13\) Lopinavir/ritonavir treatment was associated with substantial clinical benefit among severe acute respiratory syndrome coronavirus (SARS-CoV) infected patients.\(^14,15\) However, previous study reported that lopinavir/ritonavir may have hepatotoxicity in HIV patients.\(^12,16\) A total of 9.1% of HIV antiretroviral-experienced patients who received lopinavir/ritonavir treatment developed liver enzyme elevation.\(^12\) Five patients were treated with lopinavir/ritonavir in the present study. Whether the abnormalities of liver function are induced by antiviral drugs for COVID-19 such as lopinavir/ritonavir is not clear yet. Xu et al\(^17\) reported the pathological findings of COVID-19 associated with acute respiratory distress syndrome and the liver biopsy specimens of the patient presented moderate microvesicular steatosis and mild lobular and portal activity which indicated that the injury could have been caused by either severe acute respiratory syndrome coronavirus-2 infection or drug-induced liver injury. Thus, the pathogenesis of the liver injury in COVID-19 patients with chronic HBV infection deserves further investigation.

Systemic corticosteroids are recommended for the treatment of COVID for possible benefit by reducing inflammatory-induced lung injury, especially for the critically ill patients.\(^4,18\) In the study by Guan et al, corticosteroid treatment was given to 18.6% of COVID-19 patients, with a higher percentage among those with severe disease (44.5%) than nonsevere disease (13.7%).\(^7\) In the present study, two patients (28.6%) were given corticosteroids treatment. Several studies have demonstrated that the corticosteroids may increase the risk of hepatitis flare in patients with chronic HBV infection.\(^19,20\) Although, hepatitis flare was not observed in the present study, corticosteroids should be used prudently in COVID-19 patients with chronic HBV infection and close monitoring for hepatitis flare is needed.

There are several limitations to this study. First, our study was limited by a small sample size with only seven patients included. The findings need to be confirmed by a larger sample study. In addition, only half of the patients were tested for HBV markers. Thus, the prevalence of HBV infection of COVID-19 patients in our cohort may be underestimated and the potential selection bias may exist in our study. Moreover, the risk factors of abnormalities of liver function could not be analyzed due to the limitation of the sample size. Last, the impacts of COVID-19 on the HBV replication deserve further investigation since the dynamic changes of serum HBV markers were not available and only one patient was positive for hepatitis B virus e-antigen.

To the best of our knowledge, this is the first study which describes the clinical features of COVID-19 patients with chronic HBV infection. Our study indicates that the abnormalities of liver function

| Characteristics (n [%] or median [IQR]) | Without chronic HBV infection (n = 21) | With chronic HBV infection (n = 7) | P value |
|---------------------------------------|---------------------------------------|-----------------------------------|---------|
| Age, y                                | 49.0 (38.5, 54.5)                     | 47.0 (34.0, 49.0)                 | .431    |
| Male                                  | 12 (57.1)                             | 6 (85.7)                          | .172    |
| Onset symptoms                        |                                       |                                   |         |
| Fever                                 | 17 (81.0)                             | 7 (100)                           | .212    |
| Cough                                 | 13 (61.9)                             | 5 (71.4)                          | .649    |
| Laboratory tests                      |                                       |                                   |         |
| White blood cells (×10^9/L)           | 4.8 (4.0, 5.7)                        | 4.9 (4.1, 5.9)                    | .937    |
| Lymphocyte (×10^9/L)                  | 1.4 (0.9, 1.7)                        | 1.3 (0.9, 1.7)                    | .895    |
| PLT (×10^9/L)                         | 178.0 (143.0, 277.0)                  | 150.0 (96.0, 210.0)               | .160    |
| ALT, U/L                              | 31.0 (19.3, 58.5)                     | 31.0 (29.0, 38.0)                 | .469    |
| AST, U/L                              | 28.0 (23.0, 36.0)                     | 31.0 (29.0, 38.0)                 | .623    |
| Tbil, μmol/L                          | 10.9 (7.4, 17.1)                      | 12.7 (11.1, 16.6)                 | .797    |
| Albumin, g/L                          | 39.5 (38.4, 41.4)                     | 43.4 (35.3, 44.7)                 | .459    |
| PT, s                                  | 12.1 (11.8, 13.0)                     | 13.1 (12.9, 13.7)                 | .006    |
| Chest CT findings                     |                                       |                                   |         |
| Pneumonia                             | 20 (95.2)                             | 7 (100)                           | .557    |
| Outcome                               |                                       |                                   |         |
| Hospital stay, d                      | 18.0 (15.0, 23.0)                     | 15.0 (13.0, 17.0)                 | .081    |
| ICU admission                         | 2 (9.5)                               | 0                                  | .397    |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; COVID-19, coronavirus disease 2019; CT, computed tomography; HBV, hepatitis B virus; ICU, intensive care unit; IQR, interquartile range; Tbil, total bilirubin; PT, prothrombin time.
are not uncommon on COVID-19 patients with chronic HBV infection. However, no patient developed severe liver injury during hospitalization. Clinicians should increase their awareness of liver injury and closely monitor the liver function of hospitalized COVID-19 patients especially for patients with chronic HBV infection.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
All authors contributed to this study at different levels. All authors read and approved the final version. Study concept and design: CW, RH, and XY; acquisition of data: YL, CL, CZ, LZ, FJ, LL, TX, BZ, LX, XY; analysis and interpretation of data: JW and RH; drafting of the manuscript: RH and JW; critical revision of the manuscript for important intellectual content: CW, RH, and XY.

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