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Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection

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BACKGROUND & AIMS: Coronavirus disease 2019 (COVID-19) is a major global health threat. We aimed to describe the characteristics of liver function in patients with SARS-CoV-2 and chronic hepatitis B virus (HBV) coinfection.

METHODS: We enrolled all adult patients with SARS-CoV-2 and chronic HBV coinfection admitted to Tongji Hospital from February 1 to February 29, 2020. Data of demographic, clinical characteristics, laboratory tests, treatments, and clinical outcomes were collected. The characteristics of liver function and its association with the severity and prognosis of disease were described.

RESULTS: Of the 105 patients with SARS-CoV-2 and chronic HBV coinfection, elevated levels of liver test were observed in several patients at admission, including elevated levels of alanine aminotransferase (22, 20.95%), aspartate aminotransferase (29, 27.62%), total bilirubin (7, 6.67%), gamma-glutamyl transferase (7, 6.67%), and alkaline phosphatase (1, 0.95%). The levels of the indicators mentioned above increased substantially during hospitalization (all P < .05). Fourteen (13.33%) patients developed liver injury. Most of them (10, 71.43%) recovered after 8 (range 6-21) days. Notably the other, 4 (28.57%) patients rapidly progressed to acute-on-chronic liver failure. The proportion of severe COVID-19 was higher in patients with liver injury (P = .042). Complications including acute-on-chronic liver failure, acute cardiac injury and shock happened more frequently in patients with liver injury (all P < .05). The mortality was higher in individuals with liver injury (28.57% vs 3.30%, P = .004).

CONCLUSION: Liver injury in patients with SARS-CoV-2 and chronic HBV coinfection was associated with severity and poor prognosis of disease. During the treatment of COVID-19 in chronic HBV-infected patients, liver function should be taken seriously and evaluated frequently.

Keywords: SARS-CoV-2; COVID-19; HBV; Liver Injury.
aminotransferase (AST) during disease progression have been reported. However, the exact cause of preexisting liver conditions had not been outlined in these studies.

Hepatitis B virus (HBV) infection correlated with the development of cirrhosis, liver failure, and hepatocellular carcinoma remains a major public health problem worldwide. The prevalence of hepatitis B surface antigen (HBsAg) was estimated to be 5%-6% in the general population, with about 70 million cases of chronic HBV infection in China. A recent report indicated that SARS-CoV-2 might mainly act on lymphocytes, especially T lymphocytes. In the course of HBV infection, HBV-specific T lymphocytes play an important role in viral clearance and liver inflammation. Functional and quantitative defects in the HBV-specific T-cell response are associated with viral persistence. Whether the existence of HBV would affect the SARS-CoV-2 infection remains unknown. Would SARS-CoV-2 infection in patients with chronic HBV infection lead to deterioration of liver function? The characteristics of liver function in patients with SARS-CoV-2 and chronic HBV coinfection have not been reported yet.

In this study, we aimed to describe the characteristics of liver function and its association with severity and prognosis in patients with SARS-CoV-2 and chronic HBV coinfection to provide evidence for the clinical treatment of these specific patients and contribute to improving their prognosis.

**Methods**

**Study Design and Participants**

This is a single-center, retrospective study of 105 patients with SARS-CoV-2 and chronic HBV coinfection hospitalized at Tongji Hospital. Tongji Hospital is one of the major comprehensive medical treatment centers assigned for the treatment for COVID-19 patients by the government. We recruited inpatients from February 1 to February 29, 2020 who had been diagnosed as having COVID-19 and chronic HBV infection according to World Health Organization interim guidance and American Association for the Study of Liver Diseases guidelines. All patients had a history of chronic HBV infection and were tested positive for HBsAg at admission. Laboratory confirmation of COVID-19 was performed by the local health authority as previously described. The ethics committee of Tongji Hospital approved this study (TJ-IRB20200225).

**Data Collection**

Data extraction was performed by a trained team of physicians using a standardized form to collect data on demographic characteristics, duration from illness onset to hospitalization, underlying chronic medical conditions, symptoms from onset to admission, continuous laboratory test results, treatments, complications, and outcomes from electronic medical records. The information on anti-HBV treatment was collected from medical history. HBV serologic markers were tested using commercially available microparticle enzyme immunoassay kits (AxSYM; Abbott Laboratories, Abbott Park, IL). HBsAg >0.05 IU/mL was considered HBsAg-positive. Hepatitis B virus e antigen (HBeAg) <1 IU/mL and ≥1 IU/mL meant HBeAg-negative and HBeAg-positive, respectively.

Severe illness of COVID-19 was defined as one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or oxygen saturation ≤93% on room air. Liver test abnormalities were defined by the abnormality of the following indices in serum: ALT >41 U/L, AST >40 U/L, gamma-glutamyl transferase (γ-GT) >71 U/L, alkaline phosphatase (ALP) >130 U/L, or total bilirubin (TBIL) >26 μmol/L. Liver injury was defined as ALT and/or AST over 3× upper limits of normal (ULN) and/or TBIL over 2× ULN. Acute-on-chronic liver failure (ACLF) was defined as TBIL ≥5 mg/dL (85 μmol/L) and coagulopathy (international normalized ratio [INR] ≥1.5 or prothrombin activity <40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, according to the Asian Pacific Association for the Study of the Liver. Acute respiratory distress syndrome was defined according to the Berlin definition. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition. Acute cardiac injury was defined as the serum levels of hypersensitive troponin I above 34.2 pg/mL or new abnormalities shown in electrocardiography and echocardiography.

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**What You Need to Know**

**Background**

We described the characteristics of liver function and its association with severity and prognosis in patients with SARS-CoV-2 and chronic hepatitis B virus (HBV) coinfection.

**Findings**

Patients with SARS-CoV-2 and chronic HBV coinfection who developed liver injury were more likely to have severe illness and worse prognosis including higher mortality and incidence of complications such as acute-on-chronic liver failure, acute cardiac injury, and shock.

**Implications for patient care**

Liver function should be evaluated more frequently in patients with SARS-CoV-2 and chronic HBV coinfection, especially within 1 week after admission.
**Statistical Analysis**

Values are presented as number (%) for categorical variables and median (interquartile range [IQR]) for continuous variables, respectively. The differences of categorical variables between patients with and without liver injury were compared by χ² test or Fisher exact test when appropriate, and continuous variables were compared by using Wilcoxon tests. A P value less than .05 was considered statistically significant. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

**Results**

Of the 105 patients with SARS-CoV-2 and chronic HBV coinfection, 14 (13.33%) had liver injury, and 4 (3.81%) developed ACLF during the hospitalization.

**Clinical Characteristics**

The median age of these patients was 62 years (IQR, 51–70), and 55 patients (52.38%) were male. The most common symptoms from onset to admission were fever (85, 80.95%) and cough (81, 77.14%), followed by dyspnea (51, 48.57%) and fatigue (36, 34.29%). Forty-two patients (40%) had comorbidities, with hypertension (27, 25.71%) being the most common comorbidity. Five patients (4.76%) had malignancy, and 1 patient (0.95%) had hepatocellular carcinoma. Two patients (1.90%) had cirrhosis. No patient had human immunodeficiency virus coinfection, and only 1 patient (0.95%) had hepatitis C virus infection. Thirteen patients (12.38%) took nucleotide/nucleoside analogues therapy against HBV, including 9 (8.57%) with entecavir, 3 (2.86%) with tenofovir, and 1 (0.95%) with lamivudine and adefovir. A majority of patients (102, 97.14%) were tested negative for HBeAg. Fifty-six patients (53.33%) were severe COVID-19 cases. The median interval from onset to hospitalization was 10 days (IQR, 7–18).

Liver injury was more common in male patients than in female patients (92.86% vs 46.15%, P = .001). The proportion of fever was higher in patients with liver injury (P = .011). Levels of HBsAg and HBV core antibody were not significantly different in the 2 groups (both P > .05). The proportion of severe COVID-19 was higher in patients with liver injury (P = .042) (Table 1).

**Liver Function at Admission and During Hospitalization**

Elevated levels of liver tests were observed in several patients at admission, with elevated ALT, AST, TBIL, ALP, and γ-GT in 22 (20.95%), 29 (27.62%), 7 (6.67%), 1 (0.95%), and 7 (6.67%) patients, respectively. Among the patients with liver test abnormalities, most were mildly elevated within 1–2× ULN at admission. Fourteen patients (13.33%) presented with reduced prothrombin activity (65; IQR, 55–70) and prolonged INR (1.33; IQR, 1.28–1.52) at admission.

By comparing the peak value of liver tests during hospitalization with the value at admission, the levels of ALT, AST, TBIL, ALP, and γ-GT increased substantially during hospitalization (all P < .05). The proportion of ALT abnormalities and ALT over 3× ULN increased after admission (P = .021) (Table 2).

**Treatments During Hospitalization and Clinical Outcomes**

Antiviral therapy, including arbidol, lopinavir/ritonavir, interferon, and ribavirin, were given to nearly all patients (102, 97.14%). More patients received interferon atomization therapy in liver injury group (P = .018). Methylprednisolone and oxygen therapy were given to more patients with liver injury (P = .016 and .031, respectively). ACLF, acute cardiac injury, and shock happened more frequently in patients with liver injury (all P < .05). Up to March 10, 2020, 43 patients (40.95%) were still hospitalized; 55 patients (52.38%) had been discharged, and 7 patients (6.67%) died. The mortality was significantly higher in individuals with liver injury (28.57% vs 3.30%, P = .004) (Table 3).

**Course of Illness in Patients With Liver Injury**

Fourteen patients (13.33%) developed liver injury during hospitalization. The interval from onset to hospitalization of patients with liver injury was 9.5 days (IQR, 8–13). Thirteen patients (92.86%) developed liver injury within 1 week of admission. Liver tests of most patients (10, 71.43%) recovered normality after 8 days (range, 6–21). However, the other 4 patients (28.57%) rapidly progressed to ACLF, and all of them died of multiple organ failure (Figure 1).

The peak values of ALT, AST, TBIL, ALP, and γ-GT in the 4 patients with ACLF were 101.75 ± 66.64 U/L, 113.50 ± 60.58 U/L, 119.7 ± 15.94 μmol/L, 115.25 ± 21.93 U/L, and 132.00 ± 80.56 U/L, respectively. All of them developed ascites. None of them suffered encephalopathy and underwent autopsy.

**Discussion**

In the present study, we found that liver test abnormalities were relatively common in patients with SARS-CoV-2 and chronic HBV coinfection, and the levels of ALT, AST, TBIL, ALP, and γ-GT increased substantially during hospitalization. A small portion of patients developed liver injury. Patients with liver injury were more likely to have severe illness and worse prognosis including higher mortality and incidence of complications.

The present study reported evidence of liver injury in patients with SARS-CoV-2 and chronic HBV coinfection.
Several patients had various abnormal liver tests. According to previous studies, the incidences of ALT and AST abnormalities were 14.34%–29.5% and 17.9%–35%, respectively,2,4,5,16 which were similar to ours. Liver injury occurred in 21.5% of patients with COVID-19 during hospitalization as Cai et al17 reported, which was higher than that in our study (13.33%). Several reasons may explain this. First, the 2 studies used different criteria for liver injury. We defined ALT and/or AST over 3 ULN and/or TBIL over 2 ULN as liver injury according to the protocol for prevention, diagnosis, and treatment of liver injury in COVID-19,11 whereas liver injury was defined as ALT and/or AST over 3 ULN and ALP, g-GT, and/or TBIL over 2 ULN in the study of Cai et al. Second, the interval from onset to admission of patients in the present study was 10 days, which may lead to missed diagnosis of early liver injury for lack of data before admission. Furthermore, there is heterogeneity in the population characteristics included in the 2 studies.

Whether liver injury in COVID-19 is worth taking seriously remains controversial.18,19 A recent study showed the presence of abnormal liver tests and liver injury were associated with the progression to severe pneumonia.17 In our study, patients with liver injury were more likely to have severe illness and worse prognosis including higher mortality and incidence of complications such as ACLF, acute cardiac injury, and shock. Liver injury happened to most patients within 1 week, and they recovered normality after several days. However, 4 chronic HBV-infected patients deteriorated rapidly after SARS-CoV-2 coinfection with progressively elevated jaundice, coagulation dysfunction, and ascites and were diagnosed with ACLF. Eventually, they all died of multiorgan failure. Those with liver injury but no coagulation dysfunction generally went on to recover. These findings indicate that liver injury in patients with SARS-CoV-2 and chronic HBV coinfection was associated with disease severity and worse prognosis. Liver function should be evaluated more frequently in these special individuals, especially within 1 week after admission. Once liver injury occurs in patients with COVID-19, they should be treated timely to prevent poor prognosis, particularly for those with coagulation dysfunction.

### Table 1. Basic Characteristics of Patients With SARS-CoV-2 and Chronic HBV Coinfection

| Variables                        | All patients (N = 105) | Liver injury (N = 14) | Non-liver injury (N = 91) | P value |
|----------------------------------|------------------------|-----------------------|---------------------------|---------|
| Age (y)                          | 62 (51–70)             | 54 (42–67)            | 63 (51–70)                | .109    |
| Sex                              |                        |                       |                           |         |
| Male                             | 55 (52.38)             | 13 (92.86)            | 42 (46.15)                | .001    |
| Female                           | 50 (47.62)             | 1 (7.14)              | 49 (53.85)                |         |
| Smoking                          | 5 (4.76)               | 0 (0.00)              | 5 (5.49)                  | .226    |
| Chronic medical illness          |                        |                       |                           |         |
| Any                              | 42 (40.00)             | 7 (50.00)             | 35 (38.46)                | .412    |
| Diabetes                         | 10 (9.52)              | 1 (7.14)              | 9 (9.89)                  | .736    |
| Hypertension                     | 27 (25.71)             | 4 (28.57)             | 23 (25.27)                | .795    |
| Coronary heart disease           | 7 (6.67)               | 1 (7.14)              | 6 (6.59)                  | .939    |
| Chronic obstructive pulmonary disease | 3 (2.86)            | 0 (0.00)              | 3 (3.30)                  | .350    |
| Malignancy                       | 5 (4.76)               | 2 (14.29)             | 3 (3.30)                  | .126    |
| Cirrhosis                        | 2 (1.90)               | 0 (0.00)              | 2 (2.20)                  | .447    |
| HBsAg, IU/mL                     | 97.42 (8.22–250)       | 33.14 (10.60–250)     | 99.88 (7.94–250)          | .949    |
| HBeAg, IU/mL                     | ≤1                     | 102 (97.14)           | 14 (100.00)               | 1.00    |
|                                  | >1                     | 3 (2.86)              | 0 (0.00)                  |         |
| HBcAb, IU/mL                     | 9.94 (9.30–10.39)      | 9.98 (9.84–10.29)     | 9.94 (9.32–10.40)         | .750    |
| Nucleotide/nucleoside analogues therapy | 13 (12.38)          | 1 (7.14)              | 12 (13.19)                | .523    |
| Symptoms from onset to admission |                        |                       |                           |         |
| Fever                            | 85 (80.95)             | 14 (100.00)           | 71 (78.02)                | .011    |
| Cough                            | 81 (77.14)             | 11 (78.57)            | 70 (76.92)                | .891    |
| Hemoptysis                       | 2 (1.90)               | 0 (0.00)              | 2 (2.20)                  | .447    |
| Dyspnea                          | 51 (48.57)             | 9 (64.29)             | 42 (46.15)                | .204    |
| Fatigue                          | 36 (34.29)             | 3 (21.43)             | 33 (36.26)                | .260    |
| Vomiting                         | 4 (3.81)               | 1 (7.14)              | 3 (3.30)                  | .523    |
| Diarrhea                         | 19 (18.10)             | 4 (28.57)             | 15 (16.48)                | .299    |
| Interval from onset to hospitalization, days | 10 (7–18)          | 9.5 (8–13)            | 12 (7–19)                 | .277    |
| Severity of COVID-19             |                        |                       |                           |         |
| Non-severe                       | 49 (46.67)             | 3 (21.43)             | 46 (50.55)                | .042    |
| Severe                           | 56 (53.33)             | 11 (78.57)            | 45 (49.45)                |         |

NOTE. Data are shown as median (interquartile range) or n (%). Boldface indicates P < .05.
COVID-19, coronavirus disease 2019; HBcAb, hepatitis B core antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Drug-induced liver injury has received more attention in recent years. Intravenous methylprednisolone was reported to be associated with acute liver injury, whereas data on the association between oral methylprednisolone and liver injury are insufficient. In the present study, more patients with liver injury received methylprednisolone, half of them received intravenous administration. Besides methylprednisolone, other drugs such as antibiotics, arbidol, lopinavir/ritonavir, interferon, and ribavirin might also cause liver injury. 

Most of the patients enrolled in this study received these drugs. No differences were observed in the use of these drugs between patients with and without liver injury except for interferon atomization therapy, which was given to more patients with liver injury. However, not all patients experienced liver injury after these treatments. Three patients experienced liver injury before methylprednisolone therapy, and 2 patients experienced liver injury before interferon atomization therapy. Therefore, the association between these drugs and liver injury could not be further analyzed in this study.

Besides drug-induced liver injury, potential multifactorial etiologies of liver injury are as follows. First, SARS-CoV-2 may act directly on the liver. Liver biopsy specimens of the patients with COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity. Both SARS-CoV-2 and SARS-CoV could bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the target cell. A preliminary study suggested that ACE2 receptor expression was enriched in cholangiocytes (not peer-reviewed). A latest ex vivo study found that human liver ductal organoids, which preserved the human-specific ACE2+ population of cholangiocytes, were permissive to SARS-CoV-2 infection and supported robust replication. Notably, the barrier and bile acid transporting functions of cholangiocytes were impaired after virus infection (not peer-reviewed).

These may explain the γ-GT elevation and consequent liver damage. Second, HBsAg-positive and hepatitis B core antibody–positive patients treated with corticosteroids were at risk for HBV reactivation (HBVr), and the anticipated incidence of HBVr ranged from <1% to >10% and was related to the dosage and course of corticosteroids treatment. The American Gastroenterological Association recommends antiviral prophylaxis for patients at high and moderate risk for HBVr undergoing immunosuppressive drug therapy but opposes routine antiviral prophylaxis for patients at low risk for HBVr.

In our study, 30 patients received methylprednisolone therapy for a short time (less than 10 days). They all had a low risk of HBVr, so most of them did not receive antiviral HBV therapy, with only 4 patients taking nucleotide/nucleoside analogue. Because of rapid deterioration of disease, none of the 4 patients with ACLF were given anti-HBV treatment with consent of the patients or their families. The liver injury of these patients might be caused by HBVr or hepatitis flare. It indicated the clinical status of chronic HBV infection should be fully evaluated in the setting of corticosteroids, and nucleotide/nucleoside analogue therapy should be taken into account to reduce the risk of HBVr or hepatitis flare. Third, ischemic hypoxic liver injury caused by inflammation might also play a role. All these need to be further studied.

There were several limitations in our study. First, the present study was a retrospective, single-center study with relatively small sample size. Second, individuals with chronic HBV infection can transition through different clinical phases. In our study, almost all patients (97.14%) tested negative for HBeAg. Most patients (79.05%) had normal ALT levels at admission, and the other patients had elevated levels of ALT. Therefore, we could infer that most patients were inactive chronic hepatitis B or chronic hepatitis B. Lack of baseline levels of ALT and HBV DNA, patients could not be grouped according to the chronic HBV infection phases. Third, only a small proportion of patients (12.38%)
received nucleotide/nucleoside analogue therapy; the impact of nucleotide/nucleoside analogue therapy on liver injury cannot be fully analyzed. Thus, the clinical features of patients with various clinical phases of chronic HBV infection after coinfection with SARS-CoV-2 and the mechanism of liver injury need to be further investigated.

In conclusion, we described the characteristics of liver function in patients with SARS-CoV-2 and chronic HBV coinfection. Patients with liver injury were more

### Table 3. Treatments During Hospitalization and Outcomes of Patients With SARS-CoV-2 and Chronic HBV Coinfection

| Treatments                  | All patients (N = 105) | Liver injury (N = 14) | Non-liver injury (N = 91) | P value |
|-----------------------------|------------------------|-----------------------|--------------------------|---------|
| Antiviral                   | 102 (97.14)            | 13 (92.86)            | 89 (97.80)               | .367    |
| Arbidol                     | 82 (78.10)             | 9 (64.29)             | 73 (80.22)               | .320    |
| Lopinavir/ritonavir         | 16 (15.24)             | 3 (21.43)             | 13 (14.29)               | .770    |
| Interferon                  | 9 (8.57)               | 4 (28.57)             | 5 (5.49)                 | .018    |
| Ribavirin                   | 8 (7.62)               | 1 (7.14)              | 7 (7.69)                 | .942    |
| Antibiotic                  | 62 (59.05)             | 11 (78.57)            | 51 (56.04)               | .111    |
| Methylprednisolone          | 30 (28.57)             | 8 (57.14)             | 22 (24.18)               | .016    |
| Intravenous                 | 9 (8.57)               | 4 (28.57)             | 5 (5.49)                 | .021    |
| Oral                        | 21 (20.00)             | 4 (28.57)             | 17 (18.68)               | .057    |
| Oxygen therapy              | 90 (85.71)             | 14 (100.00)           | 76 (83.52)               | .031    |
| Nasal cannula               | 69 (65.71)             | 8 (57.14)             | 61 (67.03)               | .474    |
| High flow nasal cannula or NIV | 15 (14.29)          | 4 (28.57)             | 11 (12.09)               | .132    |
| IMV                         | 6 (5.71)               | 2 (14.29)             | 4 (4.40)                 | .193    |

### Complications

| Complications              | All patients (N = 105) | Liver injury (N = 14) | Non-liver injury (N = 91) | P value |
|-----------------------------|------------------------|-----------------------|--------------------------|---------|
| ARDS                        | 47 (44.8)              | 8 (57.14)             | 39 (42.86)               | .317    |
| ACLF                        | 4 (3.81)               | 4 (28.57)             | 0 (0.00)                 | .001    |
| Acute cardiac injury        | 14 (13.33)             | 5 (35.71)             | 9 (8.89)                 | .019    |
| Acute kidney injury         | 4 (3.81)               | 2 (14.29)             | 2 (2.20)                 | .070    |
| Shock                       | 3 (2.86)               | 2 (14.29)             | 1 (1.10)                 | .029    |
| Duration of hospitalization, days | 22 (14–28)           | 23.5 (9–28)           | 21 (14–28)               | .769    |
| Death                       | 7 (6.67)               | 4 (28.57)             | 3 (3.30)                 | .004    |

NOTE: Data are shown as median (interquartile range) or n (%).
ACLF, acute-on-chronic liver failure; ARDS, acute respiratory distress syndrome; HBV, hepatitis B virus; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 1. Course of illness in patients with SARS-CoV-2 and chronic HBV coinfection who had liver injury. Bars represent course of illness from onset to liver tests recovery or death of each patient. ACLF, acute-on-chronic liver failure.
likely to have severe illness poor prognosis including higher rates of complications and death. During the treatment of COVID-19 in chronic HBV-infected patients, liver function should be taken seriously and evaluated frequently.

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