INTRODUCTION

Since the first COVID-19 case was reported in Wuhan, Hubei Province, China, in December 2019, coronavirus pneumonia caused by SARS-CoV-2 infection has become prevalent globally. So far, there have been almost 2 million patients infected by SARS-CoV-2, becoming a huge threat to global health. In addition to fever, dry cough, weakness and breathing difficulty, abnormal liver function may occur in considerable proportion of SARS-CoV-2-infected patients (14.8%-76.3%). Although the exact mechanism of SARS-CoV-2-induced liver injury remains unclear, liver injury may range from asymptomatic to severe, and both acute liver failure and acute-on-chronic liver decompensation have been reported in severe COVID-19 patients. However, whether SARS-CoV-2/HBV co-infection could influence liver function and the disease outcome has not been investigated. This study aimed to evaluate whether SARS-CoV-2/HBV co-infection could influence liver function and the disease outcome. All 326 confirmed COVID-19 cases in Shanghai Public Health Clinical Center (The COVID-19 designated hospital in Shanghai, China) from 20 January 2020 to 24 February 2020 were enrolled and followed up until February 29 in this study. The clinical, laboratory data and the length of stay were collected and analysed retrospectively. 20 patients with HBV co-infection (6.1%) and 306 patients (93.9%) without HBV infection showed no differences in the level of liver function parameters. However, compared with HBsAg- patients [145.4 mg/L (103.9-179.2)], HBsAg + patients had a lower level of prealbumin [(102.3 mg/L (76.2-160.2), P = .0367]. There were also no significant differences for the discharge rate and the length of stay between two groups. Taken together, we found no evidence that SARS-CoV-2/HBV co-infection could aggravate liver injury or extend duration of hospitalization.
of COVID-19-related liver damage is still unknown, the abnormal liver function was associated with severe disease and mortality risk in COVID-19 patients. Hepatitis B virus (HBV) has a worldwide distribution and remains a leading public health problem, with a high prevalence of HBsAg at about 6.0% in China. Huang reported SARS patients with HBV infection were more prone to develop higher degree of liver injury and severe hepatitis; however, the data of the prevalence of SARS-CoV-2/HBV co-infection in COVID-19 patients are still absent. In our previous study (138 cases), there were only 9 (6.1%) cases (too small) with underlying liver diseases, so no further analysis was made over the clinical features of COVID-19 patients with HBV infection. In view of the current pandemic of SARS-CoV-2, the clinical characteristics of SARS-CoV-2 co-infection with HBV should be identified. In this retrospective study, we expanded the sample size and aimed to evaluate the influence of SARS-CoV-2/HBV co-infection on the clinical characteristics including liver function and disease outcome.

2 | METHODS

2.1 | Study design and participants

This is a retrospective, single-centre study. A total of 326 patients with SARS-CoV-2-positive results, admitted to Shanghai Public Health Clinical Center (SHPHC) from 20 January 2020 to 24 February 2020, were included and followed up until February 29. The clinical criteria of diagnosis and discharge refer to the standards for ‘Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia’ (trial version 6).

2.2 | Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Shanghai Public Health Clinical Center (2019-S047-02, Review date: January 13, 2020) and was exempted from the need for informed consent from patients.

2.3 | Data collection

The basic information and clinical characteristics of patients, including demographic, clinical, laboratory data and the length of stay, were collected by electronic medical records.

2.4 | Statistical analysis

The continuous data were presented as the mean ± standard deviation (SD), median and interquartile range (IQR), as appropriate. The independent sample t test or Mann-Whitney U test was used to compare the differences between two groups; the categorical variables were expressed by frequency and percentage, and compared by the chi-square test or Fisher exact test. P < .05 was determined as with statistically significant differences. Statistical analysis software Graphpad prism 6 was used for all analyses in this study.

3 | RESULTS

Of the 326 patients, 20 cases (6.1%) were HBV infected (HBsAg-positive, HBeAg-negative with undetectable HBV viral load (VL < 100 IU/mL; iCycler device, Bio-Rad, USA; lower limit of quantification: 100 IU/mL). As shown in Table 1, 20 patients with HBV co-infection (6.1%) and 306 patients (93.9%) without HBV infection did not show any differences regarding age and gender distribution (P>.05). There were also no differences in the level of liver function parameters, including ALT, AST, ALP, L-γ-GT, LDH, TB, DB, albumin and globulin. However, compared with HBsAg- patients [145.4 mg/L (103.9-179.2)], HBsAg+ patients had a lower level of prealbumin [102.3 mg/L (76.22-160.2), P = .0367]. 2 cases (10%) developed into severe/critically ill in HBsAg- group, while 24 cases (7.8%, P = .667) developed into severe/critically ill in HBsAg+ group. 3 cases died in the HBsAg- group, and none in the HBsAg+ group, so there was no statistical comparison. As of 29 February 2020, 19 patients (95%) in HBsAg+ patients were cured and discharged, and the length of hospital stay was 14 days (10-19). In HBsAg- patients, 245 cases (80%) were discharged with the median hospital stays of 14 days (11-19). Neither the discharge rate nor length of stay shows any difference between the two groups.

4 | DISCUSSION

Although alveolar type II(ATII) cells in lung have been served as putative main targets of viral infection, there is still a presumption that several cell types in other humoral organs can be attacked by SARS-CoV-2. As for liver, the abundant protein levels of ACE-2, a functional receptor of SARS-CoV-2, in bile ducts have been observed. In addition, a recent study based on the analysis of online single-cell RNA sequencing data from healthy liver tissues also confirmed that the level of ACE-2 mRNA in bile duct cells is comparable to ATII cells, but not in hepatocytes. These results suggest that abnormal liver function may be caused by SARS-CoV-2 preferentially binding to cholangiocytes. However, according to recent reports, the bile duct injury-related specific index, such as ALP, was not frequently elevated in COVID-19 patients. In general, whether SARS-CoV-2 can directly infect liver cells and leads to the abnormal liver function is a controversial issue due to the absence of histological evidence of COVID-19 patients. According to our recent study, we found elevated ALT and AST were more common in COVID-19 patients with abnormal liver function and liver damage can also occur in mild COVID-19 patients without any related medications before hospitalization. There is a reason to believe SARS-CoV-2 may attack the liver.
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Taken into consideration that viral co-infection can exacerbate liver injury thus have a big impact on disease progression and outcome\textsuperscript{11,12}, we investigated the prevalence of HBV infection in COVID-19 patients and found that there was a comparable rate of SARS-CoV-2/HBV co-infection to that of general population (6.1% vs 6%). These observations suggested that SARS-CoV-2/HBV co-infection is common in COVID-19 patients, although we could not assess whether existence of HBV infection increases susceptibility to SARS-CoV-2 infection.

As for liver function parameters, there were no significant differences in related indices, except for the prealbumin, which is frequently measured as indicators of liver reserve and more sensitive than other indicators. The level of prealbumin was lower in patients with co-infection than that in the control group, which indicates that the liver reserve capacity was weak in COVID-19 patients with HBV co-infection. So in our study, no evidence showed coexistence of HBV infection increases the liver injury in COVID-19 patients.

The outcomes of COVID-19 patients with/without HBV infection were also compared in our current study, and SARS-CoV-2/HBV co-infection had no effect on the course and prognosis of COVID-19, including the rates of severe/critically ill, mortality and discharged and hospital stays.

However, previous study\textsuperscript{12} indicated SARS-CoV may aggravate liver injury and activation of HBV wild strain in patients with hepatitis B virus infection. There may be essential differences in the damage to the liver of two viruses. In addition, the results of our report may be related to the immune state of SARS-CoV-2/HBV co-infection patients. All 20 patients were inactive carrier (HBeAg-negative and undetectable HBV viral load) and had not taken antiviral treatment for at least two years. Further studies are needed to explore the effect of HBV infection in other stages on the clinical characteristics of COVID-19.

Although this study is a single-centre, retrospective study, it is convincing as this centre is the only designated hospital for COVID-19 treatment in Shanghai, China, and a cohort of more than 300 cases were analysed. Moreover, the positive rate of HBsAg in COVID-19 patients was also close to that in the general population.

Taken together, our study is the first to elaborate on the clinical characteristics of SARS-CoV-2/HBV co-infection patients and demonstrate that the co-infection with HBV slightly affect liver function, showing no impact on the COVID-19 outcome.

TABLE 1  Clinical characteristics in patients with SARS-CoV-2/HBV co-infection

|                  | HBsAg+ (n = 20) | HBsAg− (n = 306) | P value |
|------------------|----------------|-----------------|---------|
| Age Median (IQR) | 52.5 (44-62.8) | 50.5 (36-64)    | .4769   |
| Male n (%)       | 13 (65%)       | 155 (50.7%)     | .2136   |

Liver function parameters Median (IQR)

|                      | HBsAg+          | HBsAg−          | P value |
|----------------------|-----------------|-----------------|---------|
| ALT (U/L)            | 28 (16.25-42.25) | 21 (15-35)     | .2644   |
| AST (U/L)            | 27.5 (22-42.25)  | 23 (18.5-33)    | .1645   |
| ALP (U/L)            | 60 (49.75-72)   | 56 (48-66.25)   | .2051   |
| L-γ-GT (U/L)         | 23.5 (15.5-35.25)| 24.5 (16-42)    | .4361   |
| LDH (U/L)            | 242.5 (200-265.5)| 224 (192-278)  | .702    |
| TB (μmol/L)          | 10.55 (6.825-15.73)| 8.35 (6.6-10.93)| .1406   |
| DB (μmol/L)          | 5.2 (2.975-7.03) | 3.9 (3.1-5.43)  | .1354   |
| Albumin (g/L)        | 37.88 (35.42-42.34)| 40.18 (37.42-42.76)| .2685   |
| Globulin (g/L)       | 28.4 (26.96-31.36)| 28.3 (25.67-31.22)| .5371   |
| Prealbumin (mg/L)    | 102.3 (76.22-160.2)| 145.4 (103.9-179.2)| .0367   |

Outcome

|                  | HBsAg+          | HBsAg−          | P value |
|------------------|-----------------|-----------------|---------|
| Severe/critically ill n (%) | 2 (10%) | 24 (7.8%) | .667   |
| Death n (%)      | 0               | 3 (0.98%)       | /       |
| Discharged n (%) | 19 (95%)        | 245 (80%)       | .14     |
| Hospital stays (d) | 14 (10-19) | 14 (11-19) | .83     |

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CONFLICTS OF INTEREST

All authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

CLP, HSP and YJM equally contributed to this study. HSP, CLP, YJM and SZY collected and analysed the data. CLP, HSP, YJM and CX drafted the manuscript. CJL and LHZ did critical revision of manuscript. All authors have approved the final manuscript.
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