Virologica Sinica (2020) 35:842–845
https://doi.org/10.1007/s12250-020-00276-5

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LETTER

Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 and Hepatitis B Virus Co-infection

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Received: 17 May 2020 / Accepted: 13 July 2020 / Published online: 24 August 2020

Dear Editor,

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection was first detected in Wuhan, China in late December 2019. The virus was spreading rapidly to other cities of China and accumulating cases had been reported (Li *et al.* 2020). On March 11, 2020, WHO declared the outbreak of SARS-CoV-2 as a pandemic. As of June 28, around 10 million COVID-19 cases have been reported in 216 countries or territories and the worldwide death toll has passed 490,000 according to data from WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Until now, there is no effective drug or vaccine available against SARS-Cov-2 infection.

In addition to the recent emerged SARS-CoV-2, hepatitis B virus (HBV) is one of the viruses which cause a global infection and threat public health. In worldwide, the prevalence of HBsAg is about 3.9% (Polaris Observatory 2018). According to a nationwide epidemiological survey of population whose ages range from 1 to 59 years in China, 2006, the prevalence of HBsAg was 7.2% (Liang *et al.* 2009). As SARS-CoV-2 and HBV both can cause liver damage (Fan *et al.* 2020), further understanding of the risk of SARS-CoV-2 on patients with HBV infection is urgently required in order to design an optimized treatment strategy. However, the impacts of SARS-CoV-2 infection on HBV patients are still not clear. For example, we do not yet know whether the SARS-CoV-2 infection is more severe in HBV patients and we also do not have much knowledge about the impact of SARS-CoV-2 on the course of HBV infection. In this retrospective study, we investigated the clinical characterizes of the patients coinfected with SARS-CoV-2 and HBV by analyzing the clinical records and laboratory tests of 123 COVID-19 patients admitted to Zhongnan Hospital of Wuhan University, Wuhan, China, from January 5 to February 20, 2020.

A total of 123 patients with COVID-19 were enrolled in this study, including 50 males and 73 females. The median age of total enrolled patients was 51.0 years (IQR, 35.0–66.0; range, 20–96 years). The most common

Xiaoping Chen, Qunqun Jiang and Zhiyong Ma contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12250-020-00276-5) contains supplementary material, which is available to authorized users.

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Table 1 Demographics, baseline characteristics, laboratory results, treatment and clinical outcomes of 123 COVID-19 patients with or without HBV infection.

	Total (n = 123)	With HBV infection (n = 15)	Without HBV infection (n = 108)	*P* value
Sex				**0.0469**
Female	73 (59.3%)	5 (33.3%)	68 (63.0%)	
Male	50 (40.7%)	10 (66.7%)	40 (37.0%)	
Age, median (IQR), y	51.0 (35.0, 66.0)	54.0 (39.0, 60.0)	51.0 (35.0, 66.0)	0.6127
Comorbidities	35 (28.5%)	4 (26.7%)	31 (28.7%)	1.0000
Hypertension	19 (15.4%)	1 (6.7%)	18 (16.7%)	0.4628
Cardiovascular disease	8 (6.5%)	0 (0.0%)	8 (7.4%)	0.5939
Diabetes	12 (9.8%)	1 (6.7%)	11 (10.2%)	1.0000
Malignancy	5 (4.1%)	3 (20.0%)	2 (1.9%)	0.0724
COPD	5 (4.1%)	0 (0.0%)	5 (4.6%)	1.0000
Liver cirrhosis	3 (2.4%)	2 (13.3%)	1 (0.9%)	**0.0390**
Signs and symptoms				
Fever	85 (69.1%)	8 (53.3%)	77 (71.3%)	0.2310
Fatigue	67 (54.5%)	8 (53.3%)	59 (54.6%)	1.0000
Myalgia	40 (32.5%)	3 (20.0%)	37 (34.3%)	0.7604
Cough	62 (50.4%)	4 (26.7%)	58 (53.7%)	0.0582
Dyspnea	26 (21.1%)	6 (40.0%)	20 (18.5%)	0.0859
Diarrhea	20 (16.3%)	2 (13.3%)	18 (16.7%)	1.0000
Headache	21 (17.1%)	2 (13.3%)	19 (17.6%)	1.0000
Days from illness onset to hospital, median (IQR), d	7.0 (4.0, 10.0)	7.0 (4.0, 10.0)	7.0 (4.0, 10.0)	0.9102
Laboratory results (units, normal range)				
White blood cell Count ($\times 10^9$/L, 3.5–9.5)	4.2 (3.0, 5.7)	4.4 (3.4, 5.6)	4.2 (2.9, 5.7)	0.6484
Lymphocyte count ($\times 10^9$/L, 1.1–3.2)	**0.9 (0.6, 1.3)**↓	**0.6 (0.4, 1.1)** ↓	**0.9 (0.6, 1.3)** ↓	0.0598
Neutrophil count ($\times 10^9$/L, 1.8–6.3)	2.5 (1.6, 3.8)	3.4 (2.3, 5.3)	2.5 (1.6, 3.7)	0.2091
Platelet count ($\times 10^9$/L, 125–350)	179.0 (129.0, 2250)	186.0 (104.0, 225.0)	178.5 (130.3, 225.5)	0.7020
Alanine aminotransferase (ALT) (U/L, 9–50)	22.0 (15.0, 34.5)	25.0 (16.0, 44.0)	21.5 (15.0, 32.8)	0.4418
Aspartate aminotransferase (AST) (U/L, 15–40)	25.0 (19.0, 38.0)	28.0 (19.0, 58.0)	25.0 (19.0, 37.0)	0.6327
Total bilirubin (TBIL) (mmol/L, 5–21)	9.6 (7.8, 12.8)	13.2 (10.0, 17.4)	9.4 (7.6, 12.3)	**0.0178**
Gamma-glutamyltransferase (GGT) (U/L, 8–57)	22.0 (15.0, 36.0)	20.0 (14.0, 28.0)	22.0 (15.3, 36.8)	0.5110
Alkaline phosphatase (ALP) (U/L, 30–120)	66.0 (54.0, 83.0)	76.0 (52.0, 102.0)	65.0 (54.0, 79.8)	0.2339
Albumin (g/L, 40–55)	38.2 (34.4, 41.0) ↓	36.0 (30.9, 39.6) ↓	38.3 (34.6, 41.1) ↓	0.2309
Prothrombin time (s, 9.4–12.5)	12.7 (11.7, 13.3) ↑	13.0 (11.5, 13.9) ↑	12.7 (11.8, 13.3) ↑	0.2376
Activated partial thromboplastin time (s, 25.1–36.5)	30.7 (28.5, 32.6)	30.6 (27.9, 32.7)	30.9 (28.6, 32.6)	0.4557
International normalized ratio (0.85–1.15)	1.2 (1.1, 1.2) ↑	1.2 (1.1, 1.3) ↑	1.2 (1.1, 1.2) ↑	0.2324
D-dimer (mg/L, 0–500)	204.0 (126.0, 464.0)	270.0 (101.0, 2139.0)	195.5 (128.0, 438.8)	0.4794
Creatinine (μmol/L, 64–104)	62.9 (52.6, 76.9) ↓	65.4 (59.0, 81.1)	61.9 (52.4, 73.5) ↓	0.2177
Severe type	33 (26.8%)	7 (46.7%)	26 (24.1%)	0.1152
Treatment				
Oxygen support	74 (60.2%)	8 (53.3%)	66 (61.1%)	0.5842
Antiviral therapy	90 (73.2%)	8 (53.3%)	82 (75.9%)	0.1152
Antibiotic therapy	123 (100.0%)	15 (100.0%)	108 (100.0%)	–
Use of corticosteroid	61 (49.6%)	5 (33.3%)	56 (51.9%)	0.2704
Hospital stays, median (IQR), days	14.0 (9.0, 20.0)	14.0 (11.0, 18.0)	14.0 (9.0, 21.0)	0.9383
Clinical outcome				
Remained in hospital	8 (6.5%)	2 (13.3%)	6 (5.6%)	0.0690
Discharged	110 (89.4%)	11 (73.4%)	99 (91.6%)	
Death	5 (4.1%)	2 (13.3%)	3 (2.8%)	

Bold represents the significant difference of *P* values less than 0.05

The arrow ↓: decrease; ↑: increase

symptoms at the onset of illness were: fever (37.4–39.1 °C, 69.1%), fatigue (54.5%), cough (50.4%), and myalgia (32.5%) (Table 1). Other symptoms included dyspnea (21.1%), headache (17.1%) and diarrhea (16.3%). Among 123 enrolled patients, thirty-five (28.5%) cases had at least one underlying comorbidity such as hypertension, cardiovascular disease, diabetes, malignancy, COPD or liver cirrhosis. Around 12.2% (15/123) of patients were also suffering from HBV infection. There were more males than females (10:5) co-infected with HBV and SARS-CoV-2 ($P = 0.0469$, Table 1). The treatment for COVID-19 patients was mainly supportive. Ninety patients were given the antiviral (oral arbidol and/or lopinavir). Seventy-four patients were offered with oxygen support and antibiotic therapy (both orally and intravenous). Sixty-one patients received corticosteroids to suppress an excessive inflammatory activation. There is no significant difference of treatments between patients with and without HBV infection (Table 1).

Laboratory results indicated that the level of total bilirubin was higher in patients with HBV infection ($P = 0.0178$, Table 1). The blood counts of the patients with or without HBV infection showed lymphopenia ($< 1.3 \times 10^9$/L, Table 1). Fifteen COVID-19 patients were examined to be HBsAg positive (5 females and 10 males). The data of anti-HBsAg, HBeAg, anti-HBeAg and anti-HBcAg were available for 11 patients with 10 HBeAg negative and one positive. HBV-DNA was detected in 13 patients. The HBV-DNA level of 10 patients was more than 20 IU/mL. Among the 15 patients, two patients have cirrhosis; three patients were treated with nucleoside analogue (oral entecavir, 0.5 mg, once daily) during the retrospective investigation period (Table 2).

Among 15 COVID-19 patients with HBV infection, 11 patients (73.4%) were discharged from the hospital according to the guideline; two patients (13.3%) were still hospitalized and the other two patients (13.3%) were dead. The causes of death are upper gastrointestinal bleeding and Intestinal bleeding respectively (Supplementary Table S1). In the group of 108 COVID-19 patients without HBV infection, ninety-nine patients (91.6%) were discharged from hospital while 6 patients (5.6%) were still hospitalized. Three patients (2.8%) without HBV infection were dead due to respiratory failure (Table 1, Supplementary Table S1). The detailed information of five dead patients was shown in Supplementary Table S1.

In line with previous observations (Chen *et al.* 2020; Guan *et al.* 2020; Huang *et al.* 2020; Shi *et al.* 2020; Wang *et al.* 2020; Xu *et al.* 2020; Yang *et al.* 2020; Zhang *et al.* 2020), we found that in COVID-19 cases without HBV infection about 50.9% (55/108) patients have the dysfunction of liver symptoms by measuring the level of ALT, AST, TBIL, GGT, and ALP during the disease progress.

Furthermore, we uncovered patients with HBV infection had a higher rate of liver cirrhosis ($P = 0.0390$, Table 1). Seven of 15 patients (46.7%) with HBV infection

Table 2 Hepatitis B serological markers, cirrhosis and nucleoside analogue use of COVID-19 patients co-infected with HBV.

Patient	Age (years)	Sex (female/male)	HBsAg (Pos/Neg)	Anti-HBs (Pos/Neg)	HBeAg (Pos/Neg)	Anti-HBe (Pos/Neg)	Anti-HBc (Pos/Neg)	HBV-DNA (IU/mL, < 20)	Cirrhosis	Use of nucleoside analogue
1	38	Male	**Pos**	NA	NA	NA	NA	**100.0**		
2	54	Male	**Pos**	NA	NA	NA	NA	NA		
3	74	Male	**Pos**	Neg	Neg	**Pos**	**Pos**	< 20	Yes	Yes
4	36	Female	**Pos**	Neg	Neg	Neg	**Pos**	**211.0**		
5	48	Male	**Pos**	Neg	Neg	**Pos**	**Pos**	**235.0**		
6	60	Male	**Pos**	Neg	Neg	**Pos**	**Pos**	< 20		
7	72	Female	**Pos**	Neg	Neg	**Pos**	**Pos**	**40,500.0**		
8	56	Female	**Pos**	Neg	Neg	**Pos**	**Pos**	**40.6**		Yes
9	57	Male	**Pos**	NA	NA	NA	NA	NA		
10	39	Male	**Pos**	NA	NA	NA	NA	**657.0**		
11	50	Female	**Pos**	Neg	Neg	**Pos**	**Pos**	**2180.0**		
12	49	Male	**Pos**	Neg	Neg	**Pos**	**Pos**	**89.0**		
13	59	Male	**Pos**	Neg	Neg	**Pos**	**Pos**	< 20		
14	77	Male	**Pos**	Neg	Neg	**Pos**	**Pos**	**166.0**	Yes	Yes
15	28	Female	**Pos**	Neg	**Pos**	Neg	**Pos**	**1340.0**		

Bold indicates the value of HBV-DNA >20 IU/mL and is considered as positive

NA Data not available, *Pos* positive; *Neg* negative

developed to the severe situation while the percentage of severe cases was much lower (24.1%) in the COVID-19 patients without HBV infection. Two of seven severe HBV and SARS-CoV-2 coinfection patients had cirrhosis whereas the percentage was one out of 26 in the cases of severe COVID-19 without HBV infection.

In the enrolled cases, we also discovered that there was a higher incidence of abnormal liver function (27/33, 81.8%) in severe COVID-19 patients than did in mild cases (43.3%, 39/90, data not shown), which agrees with the study that lower incidence of AST abnormality was found in the cases diagnosed by CT scan on the subclinical stage than in the COVID-19 patients who were confirmed after onset of symptom (Shi *et al.* 2020). Therefore, liver function could be considered as one factor to indicate the progress of COVID-19.

In our research, 21.8% of (7/33) COVID-19 severe patients were found to coinfect with HBV infection. It has been suggested that liver impairment in COVID-19 patients could be due to the direct attack of the virus or resulted by other causes such as drug toxicity and systemic inflammation (Zhang *et al.* 2020). Detecting the viral RNA or viral particles from liver biopsies of COVID-19 patients will be helpful to elucidate if virus can infect liver tissue. Our results pointed out that as high as 47% (7/15) of HBV patients were identified as severe COVID-19 cases. It is more likely that HBV patients would suffer from more severe situation during the disease progress when they were encountered with SARS-CoV-2 infection. In our enrolled cases, two patients with SARS-CoV-2 and HBV coinfection died on admission. One patient died from severe liver disease, haptic sclerosis. And the other died from intestinal hemorrhage, which seems to be associated with the impairment of gastrointestinal tract. More coinfection case analyses are required to further understand whether SARS-CoV-2 infection aggregates the progress of pre-existing disease and thereby cause death.

Acknowledgements This study was funded by the Zhongnan Hospital of Wuhan University Science, Technology and Innovation Seed Fund (Grant No. znpy2018007). The funders had no role in study design, data collection or analysis, decision to publish or preparation of the manuscript. The authors declared no competing interests.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights Statement This study was approved by the ethics board in Zhongnan Hospital of Wuhan University, Wuhan, China (No. 2020011). Informed consents were obtained from all patients upon admission to the Department of Infectious Diseases, Zhongnan Hospital of Wuhan University.

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