Liver damage in severe COVID-19 patients from Sichuan area

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Research Article

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Abstract

Background: COVID-19 has spread worldwide, which becomes a huge threat to human beings.

Materials: Severe COVID-19 patients from Sichuan area admitted to department of critical care medicine in Chengdu Public Health Clinical Medical Center were retrospectively enrolled. The liver function during the ICU hospitalization were record and analyzed.

Results: The severe COVID-19 patients mainly presented with respiratory symptoms such as fever, cough and dyspnea, and the incidence was higher in the elderly patients and males. ALT, AST, TB, and PT increased to varying degrees during the course of the disease, and ALB decreased. The incidence of liver dysfunction in patients taking Lopinavir/Ritonavi was significantly higher than patient who did not have it, but there was no statistical difference ($p < 0.05$). Patients taking low-dose Lopinavir/Ritonavi had a smaller effect on liver function than patients receiving normal dosage.

Conclusion: Severe COVID-19 patients have obvious liver damage early in the course of the disease and have a slower recovery. Pay attention to avoid using drugs that can aggravate liver damage while treating the primary disease. If there is no alternative drug, we can give some liver protection treatment appropriately.

Quick Look

Current Knowledge: As the 2019-nCoV is highly contagious and the transmission dynamics is still not fully understood. Little is known about the changes in liver function during the course of ICU hospitalization for COVID-19 patients.

This Paper Contributes To Our Knowledge: We found that severe COVID-19 patients have obvious liver damage early in the course of the disease and have a slower recovery. We should pay attention to avoid using drugs that can aggravate liver damage while treating the primary disease. If there is no alternative drug, we can give some liver protection treatment appropriately.

Background

Since December 8, 2019, a series of unexplained pneumonia cases appeared in Wuhan, Hubei Province, China, with clinical manifestations and chest radiography similar to viral pneumonia [1]. On January 7, 2020, the Chinese Center for Disease Control and Prevention (CDC) identified a new type of coronavirus from oropharyngeal swab specimen samples of the above patients, and it was subsequently named by the WHO as 2019-nCoV [2]. Since the outbreak of 2019-nCoV in Wuhan, China, now there are more and more confirmed cases in multiple countries. As the 2019-nCoV is highly contagious and the transmission dynamics is still not fully understood. On January 24, Sichuan Province immediately launched the first-level response to major public health emergencies, and the Chengdu Public Health Clinical Medical Center was the designated hospital for treating severe COVID-19 patients.

Coronavirus can cause multiple organ and system infections in a variety of animals. Main target organ is the respiratory system, manifested as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)[3,4]. In most of the COVID-19 patients, the clinical symptoms are mild and the prognosis is good, sometimes combined with liver, kidney and coagulation dysfunction, while some severe patients can present severe pneumonia, Acute Respiratory Distress Syndrome (ARDS) or multiple organ dysfunction (MODS). Huang

C[5]reported the clinical characteristics of 41 2019-nCoV pneumonia patients in Wuhan, China, with elevated aspartate aminotransferase (AST) levels in 15 of 41 patients(37%), including 8 of 13 ICU patients (62%) and 7 of 28 non-ICU patients(25%). Chen N[6]reported that they reviewed 99 2019-nCoV pneumonia patients in Wuhan and found that the overall mortality rate was close to 11%, of which 43 patients had different degrees of liver dysfunction, manifested by elevated alanine aminotransferase (ALT) or aspartate transaminase (AST), severe liver damage in 1 patient (ALT 7590 U/L, AST 1445 U/L).

Xu Z[7]first reported worldwide that the anatomical features through liver biopsy from COVID–19 patients showed moderate microvascular steatosis and mild active inflammation of the hepatic lobular manifold area, suggesting that the injury might be caused by SARS-CoV–2 infection or drug-induced. Therefore, analyzing the liver function changes in severe COVID–19 patients may provide some help in the management with severe COVID–19patients. A total of 30 severe COVID–19 patients from Sichuan area admitted to department of critical care medicine in Chengdu Public Health Clinical Medical Center were retrospectively enrolled, we analyzed and summarized the changes in liver function during the course of ICU hospitalization, which are reported as follows.

Methods

Research design

This study is a single-center retrospective study. Severe 2019-nCoV patients were defined as dyspnea, resting oxygen saturation $\leq 93\%$, oxygenation index $\leq 300\text{mmHg}$, or lung imaging showing lesions significant progress $> 50\%$ within 24–48 hours in intensive care unit (ICU) who need intensive care treatment. There were 30 confirmed patients admitted to the ICU of Chengdu Public Health Clinical Medical Center from Jan 21, 2020 to Feb 24, 2020 who were diagnosed with severe 2019-nCoV pneumonia. All cases were diagnosed with 2019-nCoV pneumonia according to the WHO provisional guidelines[2]. All cases denied hepatobiliary disease or liver function impairment before 2019-nCoV infection. study was approved by the medical ethics committees of Chengdu Public Health Clinical Medical Center and informed consent from the patient or legal representative was obtained.

Research methods

We collected and analyzed demographics, clinical manifestations, laboratory indicators of liver function, and treatment regimen. The liver function indicators selected mainly included ALT, AST, albumin (ALB), total Bilirubin (TB), prothrombin time (PT). The clinical results were followed up to Feb 24, 2020. The laboratory diagnosis of 2019-nCoV was confirmed by Chengdu Public Health Clinical Medical Center and Chengdu Center for Disease Control. The patient's oropharyngeal swab specimens were taken and put into the preservation solution by a dedicated outpatient physician, and then sent for RT-PCR test. The specimens were also tested for other respiratory viruses, including influenza A and B, respiratory syncytial virus, parainfluenza virus, adenovirus, herpes virus, etc. Perform chest X-ray or chest CT examination for all patients when admitted to hospital.

Statistical analysis

For continuous variables, we represent it as the mean (SD) if they fit a normal distribution, otherwise we represent it as the median (IQR) and categorical variables as counts (%). For laboratory inspection results we also evaluated whether the measured values are outside the normal range. We use SPSS (ver.17.0)for all data analysis.

Results

30 severe COVID-19 patients were included in this study. Among them, 18 were males and 12 were females, with an average age of 61 years (33–87 years). 29 cases (97%) were mainly complained of fever. Other symptoms included cough (80%), dyspnea (67%), fatigue (20%), nausea (17%). 14 patients (47%) had chronic diseases, including cardiovascular and cerebrovascular diseases, endocrine system diseases, Chronic kidney disease, rheumatic immune disease, respiratory disease, malignant tumor and nervous system disease (Table 1). Up to Feb 24, there were 2 deaths, and 8 cases are still being treated in ICU, and the other 20 patients are transferred out of the ICU, the average ICU stay in the 20 patients was 6.2 days. The laboratory indicators were selected for analysis within 1 week from the day admitted to ICU. 24 patients received different dosage of Lopinavir/Ritonavir for antiviral therapy, while 6 patients were not treated with it. There were 5 patients decreased the dosage due to gastrointestinal side effects (250mg bid), and 19 patients were treated with normal dose (500mg bid).

All patients' AST and ALT level were already at the upper limit of the normal range when they entered the ICU. They gradually increased with the progress of the disease, but the levels of TB, ALB and PT did not fluctuate greatly. ALB was always lower than normal. The PT was always higher than normal (Fig. 1).

30 patients were divided into two groups according to whether they were taking Lopinavir/Ritonavir, group A was the patient who were not given Lopinavir/Ritonavir, and group B was the patient who had it. We found that the incidence of ALT, AST, TB and PT abnormalities in group B seemed to be higher than group A, but there was no statistical difference ($p < 0.05$) (Fig. 2).

According to the different doses of Lopinavir/Ritonavir antiviral treatment, they were subdivided into normal dose group (B1) and reduced dose group (B2). Then compared the B1 and B2 group. The effects of Lopinavir/Ritonavir on liver function in group B2 (ALB and TB) were not obvious. The values of ALB and TB on the second day between B1 and B2 were statistically different ($p < 0.05$) (Fig.3, Fig.4).

Discussion

In our study, fever is the most common symptom in COVID-19 patients, of which 60% were male patients, which is consistent with previous research reports. But our patients are generally older than the previous studies, especially populations older than 80 years old [5,6,8,9]. It shows that older, male patients are more likely to be infected by 2019-nCoV, the same with the previous studied. There are currently no specific drugs to deal with the COVID-19. Most of the patients in our study received Lopinavir/Ritonavir antiviral therapy. Because of the small sample size, the efficacy of the drug cannot be analyzed.

According to previous research reports, most of the COVID-19 patients just suffer mild symptoms and almost have good prognosis. However, the mortality rate of critical COVID-19 patients was significantly higher, up to 49% [10]. Most of them were accompanied by multiple organ dysfunction, mainly involving lung, circulation, kidney, liver and myocardium [11]. 2019-nCoV, SARS-CoV and MERS-CoV are all belong to coronaviruses, which can cause different degrees of liver damage after infection [5,12,13]. Lee N [14] reported that the incidence of liver enzyme abnormalities in patients with SARS-CoV infection in Hong Kong is 23 %, and Zhao LF [15] reported that the incidence of liver function abnormalities in patients with SARS-CoV infection varies from region and the severity of the disease, which fluctuates between 21% and 66.9% and there are varying degrees of liver dysfunction, manifested by an increase in AST, ALT, and a decrease in serum ALB. In this study, 30 COVID-19 patients had

varying degrees of damage during treatment in the ICU, showing a decrease in ALB and elevated levels of AST, ALT, TB, and PT.

ALB is a protein synthesized by the liver and is an indicator of liver synthesis function. In the cases we collected, the results showed that most patients experienced a decrease in ALB on the first day when admitted to ICU, which was accompanied by the entire disease course. The 2019-nCoV virus may have direct damage to liver cells in acute phase, leading to a rapid decline of liver synthesis function. In the late stage of 2019-nCoV virus infection, the possible decline in serum proteins may be due to the subsequent effects of 2019-nCoV directly damaging liver cells, and serious consumption of the disease. Besides, liver function damage might also cause by the use of drugs such as Lopinavir/Ritonavi during treatment.

ALT and AST are two indicators used to evaluate liver function. The liver damage caused by general viral infectious diseases is mainly manifested by the increase in liver enzymes. Xu Z[7] reported the pathological and anatomical characteristics of patient who was infected with 2019-nCoV and found that the liver biopsy specimens had moderate microvascular steatosis and mild active inflammation in the hepatic lobular duct area, which suggest that the damage may be caused by 2019-nCoV infection or drug-induced liver damage. Therefore, the virus itself has certain kind damage to the liver cell. The ALT and AST of all patients who were enrolled in our research had increased when they entered the ICU, and gradually rised with the progress of the disease. However, the use of drugs such as Lopinavir/Ritonavi may also cause liver damage when we gave for antiviral treatment. We compared the liver function between two groups of patients, and one of the group received the Lopinavir/Ritonavi therapy and another group not, and we found that the abnormal incidence of ALT, AST, TB and PT in the Lopinavir/Ritonavi group seems to be higher than another group of patient who did not take it, which proves that the drug did can aggravate liver damage in severe COVID-19 patients, but there was not statistically difference, which may due to the small sample size. We then divided the patients into normal dose groups and reduction dose groups according to the different doses of Lopinavir/Ritonavi therapy. It showed that the reduction dose group had less damage effect to ALT, AST, ALB, and Tb, the ALB and TB values have statistical differences on the second day ($P < 0.05$), which further illustrates that there was a dose-dependent effect on the liver function, but the drug effect or its pharmacokinetics after reduction dose is not clear yet, and whether it has an impact on the prognosis of the disease itself is unknown.

Limitations

The research only included 30 severe COVID-19 patients, the small sample size research conclusion can only be used as a guide and cannot confirm a certain hypothesis. Hopefully the findings of this study can encourage colleagues to conduct larger sample studies or multi-center randomized controlled trials. Although this is a retrospective study, the data in the study can provide some guidance on the treatment of critically ill COVID-19 patients.

Conclusion

In conclusion, severe COVID-19 patients had obvious liver function damage early in the course of the disease, and the recovery is slow. During the clinical diagnosis and treatment, we should pay attention to the liver function, and avoid using drugs that may aggravate liver damage while treating the primary disease. If there is no alternative medicine, liver protection treatment can be given appropriately. Dynamic monitoring of liver function changes during the course of severe COVID-19 is of great significance.

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Declarations

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Author Contributions

L TL, DC, DQ, and CH collected the information that was used in this study, wrote the main manuscript text. LS, Y RM, and GY were the statistical team members, and prepared all figures and table. H XB and P LA were responsible for guidance and supervision. All authors reviewed the manuscript.

Additional Information

The authors declare that they have no conflicts of interest in relation to this study.

Tables

Table 1: Demographic and baseline characteristics of Severe COVID-19 patients

		Patients (n=30)
Age, years		
Mean (SD)		61 (17.1)
Range		33-87
30-39		4 (13%)
40-49		5 (17%)
50-59		5 (17%)
60-69		6 (20%)
70-79		3 (10%)
≥80		7 (23%)
Sex		
Female		12 (40%)
Male		18 (60%)

Signs and symptoms at admission

Fever	29 97%
Cough	24 80%
Shortness of breath	20 67%
fatigue	6 20%
Nausea	5 17%
Chronic medical illness	
Cardiovascular and cerebrovascular diseases	14 47%
Endocrine system diseases	7 23%
Chronic kidney diseases	3 10%
Rheumatic immune diseases	1 3%
Chronic respiratory system diseases	2 7%
Malignant tumors	1 3%
Nervous system diseases	2 7%

Figures

Figure 1

Line chart of liver function index changes in 30 severe COVID-19 patients.

Figure 2

The 30 patients were divided into group A and group B according to whether taking Lopinavir/Ritonavir. The figure shows the percentage of patients with abnormal liver function index every day within one week after entering ICU.

Figure 3

Dynamic changes of AST, ALT and ALB in normal dose group (B1) and halved dose group (B2) within one week after hospitalization in ICU.

Figure 4

Dynamic changes of TB and PT in normal dose group (B1) and halved dose group (B2) within one week after hospitalization in ICU