Observational Study

Medicine®

OPEN

Comparison of liver biochemical abnormality between COVID-19 patients with liver cirrhosis versus COVID-19 alone and liver cirrhosis alone

A STROBE observational study

Yang An, MS[a,b,c], Zhuang Ma, MD[a,d,e], Xiaozhong Guo, MD[a,b], Yufu Tang, MD[a,e], Hao Meng, MD[a,e], Hao Yu, MD[a,e], Chengfei Peng, MD[a,e], Guiyang Chu, MD[a,f], Xinwei Wang, MD[a,e], Yue Teng, MD[a,e], Quanyu Zhang, MD[a,e], Tianyi Zhu, MD[a,d,e], Bing Wang, MD[a,g], Zhenhua Tong, MD[a,g], Haitao Zhao, MD[a,d], Hui Lu, MD[a,e], Xingshun Qi, MD[a,b,*]

Abstract

Coronavirus disease (COVID-19) patients frequently develop liver biochemical abnormality. However, liver biochemical abnormality in COVID-19 patients with liver cirrhosis is under-recognized.

Patients hospitalized during COVID-19 pandemic in China (ie, from February to April 2020) were screened. All of 17 COVID-19 patients with liver cirrhosis consecutively admitted to the Wuhan Huoshenshan Hospital were identified. Meanwhile, 17 age-, sex-, and severity-matched COVID-19 patients without liver cirrhosis admitted to this hospital were selected as a control group; all of 14 cirrhotic patients without COVID-19 consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command were selected as another control group. Incidence of liver biochemical abnormality and decompensated events were primarily compared.

Among the COVID-19 patients with liver cirrhosis, the incidence of liver biochemical abnormality at admission and during hospitalization were 76.50% and 84.60%, respectively; 7 (41.20%) had decompensated events at admission; 1 was transferred to intensive care unit due to gastrointestinal bleeding. Among the COVID-19 patients without liver cirrhosis, the incidence of liver biochemical abnormality at admission and during hospitalization were 58.80% ($P = .271$) and 60.00% ($P = .150$), respectively. Among the cirrhotic patients without COVID-19, the incidence of liver biochemical abnormality at admission and during hospitalization were 69.20% ($P = .657$) and 81.80% ($P = .855$), respectively; 11 (78.60%) had decompensated events at admission ($P = .036$). None died during hospitalization among the three groups.

Liver biochemical abnormality is common in COVID-19 patients with liver cirrhosis. Management of decompensated events in cirrhotic patients without COVID-19 should not be neglected during COVID-19 pandemic.

Abbreviations: ACE2 = angiotensin converting enzyme 2, AKP = alkaline phosphatase, ALB = albumin, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, COVID-19 = coronavirus disease, Cr = creatinine, CRP = C-reactive protein, FiO_2 = oxygen concentration, GGT = gamma-glutamyl transpeptidase, HB = hemoglobin, ICU = intensive care unit, INR = international normalized ratio, K = potassium, MELD = model for end-stage liver disease, NA = sodium, PaO_2 = arterial blood oxygen, PLT = platelet count, PT = prothrombin time, rRT-PCR = real-time reverse-

Editor: Ritesh Kumar.

The authors have no funding and conflicts of interest to disclose.

Prior Publication: This work was partially presented as a poster presenter during 30th Asian Pacific for The Study of Liver (APASL) 2021 Virtual Meeting held in Bangkok, Thailand from 4 to 6 February 2021.

The datasets generated during and/or analyzed during the present study are not publicly available, but are available from the corresponding author on reasonable request.

[a] COVID-19 Study Group, General Hospital of Northern Theater Command, [b] Liver Cirrhosis Study Group, Department of Gastroenterology, General Hospital of Northern Theater Command, [c] Postgraduate College, Shenyang Pharmaceutical University, [d] Department of Respiratory Medicine, General Hospital of Northern Theater Command, Shenyang, [e] Wuhan Huoshenshan Hospital, Wuhan, [f] Information Section of Medical Security Center, General Hospital of Northern Theater Command, [g] Section of Medical Service, General Hospital of Northern Theater Command, Shenyang, P.R. China.

[*] Correspondence: Xingshun Qi, Department of Gastroenterology, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang, 110840, Liaoning Province, China (e-mail: xingshunqi@126.com).

How to cite this article: An Y, Ma Z, Guo X, Tang Y, Meng H, Yu H, Peng C, Chu G, Wang X, Teng Y, Zhang Q, Zhu T, Wang B, Tong Z, Zhao H, Lu H, Qi X. Comparison of liver biochemical abnormality between COVID-19 patients with liver cirrhosis versus COVID-19 alone and liver cirrhosis alone: A STROBE observational study. Medicine 2021;100:19(e25497).

Received: 19 October 2020 / Received in final form: 4 March 2021 / Accepted: 23 March 2021

http://dx.doi.org/10.1097/MD.0000000000025497

transcriptase-polymerase-chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SpO_2 = mean oxygen saturation, TBIL = total bilirubin, WBC = white blood cell.

Keywords: COVID-19, liver biochemical abnormality, liver cirrhosis, outcome, SARS-CoV-2

1. Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can lead to coronavirus disease 2019 (COVID-19), has been rapidly disseminated around the world, leading to great burden of global public health.[1] Till February 23, 2021, a total of 111, 102, 016 confirmed cases and 2, 462, 911 deaths have been reported worldwide according to the World Health Organization statistics.[2] COVID-19 is mostly acute and can quickly recover, but potentially fatal with an overall mortality of around 3%.[3]

Except for respiratory symptoms, such as fever, cough, and dyspnea,[3] COVID-19 patients often develop different degrees of liver injury.[4] Notably, COVID-19 patients with pre-existing liver diseases, especially liver cirrhosis, have a higher incidence of liver biochemical abnormality, liver injury, and even hepatic decompensation events.[5–7] On the other hand, it is assumed that liver cirrhosis is a high-risk comorbid condition for severe COVID-19 due to its inherent immune dysfunction.[8] Decompensated liver cirrhosis and acute-on-chronic liver failure are also crucial risk factors for poor prognosis of COVID-19 patients.[9,10]

It is important for hepatologists and patients to understand the impact of COVID-19 on outcomes of patients with liver cirrhosis. Herein, we conducted a retrospective case-control study to analyze the clinical characteristics, abnormal liver biochemistry, treatment options, and in-hospital outcome of COVID-19 patients with liver cirrhosis.

2. Methods

2.1. Study design

The study protocol has been approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command with an approval number [**Y (2020) 026**] and performed according to the Declaration of Helsinki.

All study investigators work at the General Hospital of Northern Theater Command in Shenyang, and some of them had voluntarily participated in the clinical management of COVID-19 patients at the Huoshenshan Hospital in Wuhan from February 2020 to April 2020. In this study, we retrospectively reviewed the medical records of 3041 COVID-19 patients who were admitted to the Wuhan Huoshenshan Hospital during this period, and 17 of them also had a previous diagnosis of liver cirrhosis. Meanwhile, we selected 17 COVID-19 patients without liver cirrhosis, who should have comparable age, sex, and severity of COVID-19 and more comprehensive clinical and laboratory data, as the first control group. Additionally, all of 14 cirrhotic patients without COVID-19, who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command from February 2020 to April 2020, were selected as the second control group. The exclusion criteria were as follows:

1. medical history was incomplete to determine a previous diagnosis of pre-existing liver cirrhosis;
2. liver biochemical examination was not available at the time of admission or during hospitalization; and
3. the in-hospital outcome was not clarified.

2.2. Clinical data collection

We collected information regarding demographic data (i.e., age and gender), comorbidities (i.e., diabetes, coronary heart disease, and hypertension), etiology of liver disease, decompensated cirrhosis events, clinical presentation (i.e., COVID-19 related symptoms and cirrhosis related complications), severity of COVID-19 at admission, and laboratory tests [i.e., hemoglobin (HB), white blood cell (WBC), neutrophils percentage, lymphocytes percentage, platelet count (PLT), C-reactive protein (CRP), total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), gamma-glutamyl transpeptidase (GGT), creatinine (Cr), sodium (NA), potassium (K), prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT)]. Child-Pugh score and model for end-stage liver disease (MELD) score were calculated.[11] The use of antiviral drugs (i.e., arbidol, lopinavir, ritonavir, and oseltamivir), antibiotics, traditional Chinese medicine, systemic corticosteroids, and intravenous immunoglobulin were recorded.

2.3. Diagnosis and definition

2.3.1. COVID-19. The diagnosis and clinical management of COVID-19 patients were in accordance with the Chinese practice guidelines.[12] SARS-CoV-2 nucleic acid positivity was confirmed in samples of sputum, nasopharynx swab, and secretions of lower respiratory tract tested by real-time reverse-transcriptase-polymerase-chain reaction (rRT-PCR) assay.[13] Moderate cases were defined as fever, respiratory symptoms and pneumonia can be seen in imaging. Severe cases were defined as any one of the following:

1. respiratory distress with respiratory rate > 30 breaths per minute;
2. mean oxygen saturation (SpO_2) $< 93\%$ on room air; or
3. arterial blood oxygen (PaO_2)/oxygen concentration (FiO_2) $\leq$ 300 mmHg.

Critical illness was defined by the presence of any one of the following:

1. admission to intensive care unit (ICU);
2. respiratory failure requiring invasive mechanical ventilation;
3. shock; or
4. other multisystem organ failure requiring ICU level of care.[12]

2.3.2. Liver cirrhosis. Liver cirrhosis was diagnosed according to the clinical manifestations, imaging, endoscopy, and history of liver cirrhosis.

2.3.3. Liver biochemical abnormality. Liver biochemical abnormality refers to abnormal liver-related biochemical indicators, including TBIL, ALT, AST, AKP, and GGT at admissions

and during hospitalizations. In detail, their cut-off values included TBIL > 26 μmol/L, AST > 45 U/L, ALT > 40 U/L, AKP > 135 U/L, and GGT > 45 U/L.

2.4. Endpoints

The length of hospitalizations, transfer to the ICU, and in-hospital deaths were observed.

2.5. Statistical analyses

Demographics, clinical characteristics, laboratory tests, treatment, and in-hospital outcome were compared between COVID-19 with liver cirrhosis group versus COVID-19 without liver cirrhosis group and liver cirrhosis without COVID-19 group. Continuous variables were expressed as mean ± standard deviation and median (range). Categorical variables were expressed as frequency (percentage). Nonparametric Mann –Whitney *U* test was used for a comparison of continuous variables and chi-square test and fisher exact tests were used for a comparison of categorical variables. All statistical analyses were performed with IBM SPSS software version 20.0 (SPSS Inc., Armonk, New York, USA). A two-sided $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of cirrhotic patients with COVID-19

Characteristics of cirrhotic patients with COVID-19 were shown in Table 1. The median age was 67.00 years old (range: 35.00–92.00). Most of them were male. Viral hepatitis was the main etiology of cirrhosis. More than half of patients had underlying comorbidities. The most common symptoms at the onset of illness were fever (52.90%), cough (58.80%), shortness of breath (58.80%), and fatigue (64.70%). Notably, 2 patients presented with hematemesis and/or melena alone without respiratory symptoms at admission. Nine and 8 patients had moderate and severe COVID-19, respectively. The median Child-Pugh and MELD scores were 6.50 (range: 5.00–9.00) and 10.00 (range: 8.00–18.00), respectively.

3.2. Abnormal liver biochemical indicators in cirrhotic patients with COVID-19

Among the abnormal liver biochemical indicators observed at admission, abnormal GGT (9/17, 52.90%) was the most common, followed by AKP (6/17, 35.30%), ALT (5/17, 29.40%), AST (4/17, 23.50%), and TBIL (3/17, 17.60%). Liver biochemical indicators were re-tested during hospitalizations in 13 patients; abnormal GGT (6/13, 46.20%) was the most common, followed by AST (4/13, 30.80%), AKP (3/13, 23.10%), TBIL (3/13, 23.10%), and ALT (2/13, 15.40%) (Fig. 1).

3.3. Treatment and outcomes in cirrhotic patients with COVID-19

Five patients had ascites, and 3 of them underwent abdominal paracentesis for tense or refractory ascites during hospitalization. Two patients with gastrointestinal bleeding received pharmaco-

Table 1

Difference of baseline characteristics between COVID-19 with liver cirrhosis versus COVID-19 without liver cirrhosis and liver cirrhosis without COVID-19.

Variables	No. Pts	COVID-19 with liver cirrhosis	No. Pts	COVID-19 without liver cirrhosis	No. Pts	Liver cirrhosis without COVID-19	$P^{\#}$ value	P^{*} value
Age (years)	17	67.00 (35.00–92.00) 65.00 ± 14.53	17	67.00 (35.00–93.00) 65.06 ± 14.76	14	56.00 (38.00–69.00) 55.86 ± 9.52	.986	.071
Sex (male) (%)	17	11 (64.70%)	17	11 (64.70%)	14	12 (85.70%)	1.000	0.183
Severity of COVID-19 (Moderate/Severe) (%)	17	9 (52.90%)/8 (47.10%)	17	9 (52.90%)/8 (47.10%)	14	NA	1.000	NA
Etiology of Liver Diseases								
HBV (%)	17	4 (23.50%)	17	NA	14	4 (28.60%)	NA	.750
HCV (%)	17	4 (23.50%)	17	NA	14	2 (14.30%)	NA	.517
Alcohol Abuse (%)	17	0 (0.00%)	17	NA	14	6 (42.90%)	NA	*.004*
Other or Unknown Etiology (%)	17	9 (52.90%)	17	NA	14	3 (21.40%)	NA	.073
Decompensated Events (%)	17	7 (41.20%)			14	11 (78.60%)		*.036*
Gastrointestinal Bleeding (%)	17	2 (11.80%)	17	NA	14	7 (50.00%)	NA	*.020*
Ascites (%)	17	5 (29.40%)	17	NA	14	9 (64.30%)	NA	.052
Hepatic Encephalopathy (%)	17	0 (0.00%)	17	NA	14	1 (7.10%)	NA	.452
Comorbidities (%)								
Diabetes (%)	17	5 (29.40%)	17	3 (17.60%)	14	2 (14.30%)	.419	.316
Coronary Heart Disease (%)	17	4 (23.50%)	17	5 (29.40%)	14	2 (14.30%)	.697	.517
Hypertension (%)	17	6 (35.30%)	17	8 (47.10%)	14	2 (14.30%)	.486	.183
Clinical Presentations								
Fever (%)	17	9 (52.90%)	17	13 (76.50%)	14	NA	.151	NA
Cough (%)	17	10 (58.80%)	17	11 (64.70%)	14	NA	.724	NA
Shortness of Breath (%)	17	10 (58.80%)	17	9 (52.90%)	14	NA	.730	NA
Fatigue (%)	17	11 (64.70%)	17	7 (41.20%)	14	1 (7.10%)	.169	*.001*
Hematemesis and/or Melena (%)	17	2 (11.80%)	17	NA	14	7 (50.00%)	NA	*.020*
Laboratory Tests at Admission								
Hemoglobin (g/L)	17	105.00 (74.00–157.00) 109.24 ± 22.36	17	134.00 (83.00–157.00) 127.59 ± 22.92	13	106.00 (54.00–137.00) 94.92 ± 31.32	*.012*	.295
White Blood Cell (10^9/L)	17	4.40 (2.50–13.50) 5.35 ± 2.89	17	5.30 (3.20–12.30) 5.92 ± 2.37	13	5.10 (1.50–6.70) 4.38 ± 1.75	.318	.691

(*continued*)

Table 1

(continued).

Variables	No. Pts	COVID-19 with liver cirrhosis	No. Pts	COVID-19 without liver cirrhosis	No. Pts	Liver cirrhosis without COVID-19	$P^{\#}$ value	P^{*} value
Platelet (10^9/L)	17	129.00 (33.00–281.00) 128.94 ± 73.33	17	221.00 (110.00–377.00) 226.18 ± 68.05	13	132.00 (35.00–278.00) 131.08 ± 71.23	*<.001*	.917
Lymphocyte (%)	17	26.90 (6.80–46.50) 24.69 ± 11.08	17	25.30 (8.50–44.60) 24.30 ± 10.61	13	30.20 (9.10–50.10) 37.66 ± 11.11	.469	.451
Lymphocyte Count (10^9/L)	17	1.12 (0.52–1.83) 1.14 ± 0.41	17	1.04 (0.62–2.81) 1.38 ± 0.67	13	0.91 (0.57–2.10) 1.09 ± 0.50	.890	.645
Neutrophil (%)	17	59.10 (38.60–88.70) 61.91 ± 12.36	17	62.10 (38.80–87.50) 64.80 ± 13.66	13	58.40 (41.40–75.60) 59.45 ± 8.31	.331	.325
Neutrophil Count (10^9/L)	17	2.89 (1.34–12.00) 3.65 ± 2.86	17	3.38 (1.80–10.82) 3.97 ± 2.35	13	3.00 (0.80–5.09) 2.61 ± 1.36	.310	.601
C-Reactive Protein (mg/L)	17	6.16 (0.04–38.86) 10.97 ± 17.36	17	4.68 (0.70–65.74) 13.58 ± 17.67	12	1.71 (0.05–23.00) 5.61 ± 7.23	.692	.330
Procalcitonin (ng/ml)	13	0.08 (0.03–0.25) 0.10 ± 0.07	14	0.05 (0.03–0.29) 0.08 ± 0.07	7	0.04 (0.02–0.21) 0.07 ± 0.07	.222	.152
Albumin (g/L)	17	36.00 (27.60–45.20) 35.68 ± 4.12	17	36.00 (26.50–40.40) 35.79 ± 4.03	14	31.40 (22.40–41.20) 31.15 ± 6.10	.630	*.030*
Elevated Albumin (%)	17	16 (94.10%)	17	16 (94.10%)	14	11 (78.60%)	1.000	.199
Total Bilirubin (μmol/L)	17	20.00 (6.30–54.10) 21.61 ± 14.22	17	10.50 (5.30–26.40) 11.54 ± 5.32	14	28.30 (10.40–44.90) 25.84 ± 11.64	*.010*	.266
Elevated Total Bilirubin (%)	17	3 (17.60%)	17	1 (5.90%)	14	7 (50.00%)	.287	.055
Alanine Aminotransferase (U/L)	17	28.20 (10.10–311.60) 46.57 ± 70.18	17	33.90 (7.60–163.80) 38.95 ± 37.04	14	23.27 (8.63–234.76) 47.45 ± 60.14	.945	.959
Elevated Alanine Aminotransferase (%)	17	5 (29.40%)	17	5 (29.40%)	14	4 (28.60%)	1.000	.419
Aspartate Aminotransferase (U/L)	17	31.80 (15.50–348.40) 53.67 ± 77.87	17	19.60 (11.10–37.90) 22.26 ± 8.46	14	34.49 (12.81–203.08) 68.34 ± 65.01	*.009*	.427
Elevated Aspartate Aminotransferase (%)	17	4 (23.50%)	17	0 (0.00%)	14	6 (42.90%)	*.033*	.252
Alkaline Phosphatase (U/L)	17	89.70 (59.10–451.30) 140.88 ± 101.74	17	67.60 (34.60–133.50) 75.70 ± 28.32	14	107.48 (49.09–508.25) 144.92 ± 143.35	*.004*	.525
Elevated Alkaline Phosphatase (%)	17	6 (35.30%)	17	0 (0.00%)	14	3 (21.40%)	*.007*	.397
Gamma-Glutamyl Transpeptidase (U/L)	17	49.90 (11.40–446.10) 108.32 ± 132.81	17	32.30 (13.10–104.80) 44.09 ± 29.90	14	54.29 (15.73–538.56) 111.01 ± 144.80	.163	.874
Elevated Gamma-Glutamyl Transpeptidase (%)	17	9 (52.90%)	17	7 (41.20%)	14	8 (57.10%)	.492	.815
Aspartate Aminotransferase/Alanine Aminotransferase ratio	17	1.20 (0.53–2.31) 1.28 ± 0.47	17	0.88 (0.36–1.22) 0.85 ± 0.23	14	1.64 (0.87–3.21) 1.69 ± 0.66	*.007*	.081
Serum Creatinine (μmol/L)	17	59.20 (43.10–126.40) 66.28 ± 26.08	17	66.30 (47.30–91.30) 69.41 ± 13.63	14	65.42 (47.77–104.50) 67.45 ± 15.00	.125	.190
Sodium (mmol/L)	17	140.70 (134.40–146.50) 139.96 ± 3.69	17	140.90 (132.20–146.50) 140.02 ± 3.45	14	139.30 (134.80–142.30) 138.92 ± 2.14	.836	.361
Potassium (mmol/L)	17	4.22 (3.59–5.42) 4.19 ± 0.50	17	4.35 (2.83–5.55) 4.23 ± 0.61	14	3.77 (3.17–4.37) 3.82 ± 0.39	.513	.052
Prothrombin Time (seconds)	14	14.94 (12.73–23.31) 15.71 ± 3.11	15	12.82 (10.23–17.11) 13.29 ± 1.89	14	15.50 (12.60–18.70) 15.76 ± 1.99	*.015*	.748
INR	14	1.24 (1.06–1.94) 1.30 ± 0.26	15	1.07 (0.93–1.43) 1.12 ± 0.14	14	1.22 (0.92–1.54) 1.24 ± 0.20	*.015*	.908
APTT (seconds)	14	31.92 (23.01–51.22) 33.46 ± 7.31	15	27.62 (23.75–33.88) 27.95 ± 3.07	14	41.70 (33.90–46.70) 40.36 ± 4.00	*.015*	*.003*
Fasting Blood Glucose (mmol/L)	17	5.48 (4.36–21.31) 6.85 ± 4.17	17	5.11 (4.13–14.58) 6.70 ± 3.40	14	6.35 (4.87–8.47) 6.39 ± 1.28	.459	.217
Liver Biochemical Abnormality at Admission (%)	17	13 (76.50%)	17	10 (58.80%)	14	9 (69.20%)	.271	.657
Child-Pugh Score	14	6.50 (5.00–9.00) 6.64 ± 1.55	17	NA	14	8.00 (5.00–10.00) 7.43 ± 1.28	NA	0.248
MELD Score	14	10.00 (8.00–18.00) 11.00 ± 3.01	17	NA	14	11.00 (7.00–14.00) 10.29 ± 2.20	NA	0.815
Length of Hospitalization (days)	17	14.00 (4.00–35.00) 15.29 ± 10.37	17	22.00 (10.00–35.00) 21.18 ± 7.03	14	8.00 (3.00–29.00) 10.93 ± 7.34	0.051	0.339
ICU (%)	17	1 (5.90%)	17	NA	14	NA	NA	NA

APTT = Activated Partial Thromboplastin Time, COVID-19 = Coronavirus Disease-19, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, ICU = Intensive-Care Unit, INR = International Normalized Ratio, MELD = Model of End-Stage Liver Disease, Pts = Patients.

$P^{\#}$: Comparison between COVID-19 with and without liver cirrhosis; P^{*}: Comparison between liver cirrhosis with and without COVID-19.

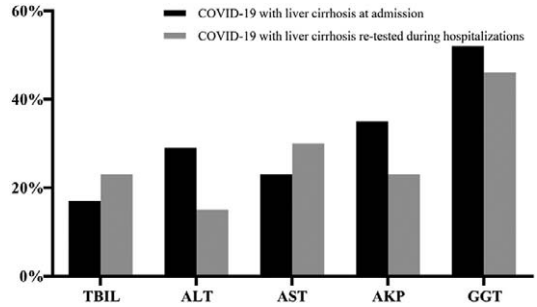

Figure 1. The incidence of abnormal liver biochemical indicators in COVID-19 with liver cirrhosis at admission and re-testing during hospitalization.

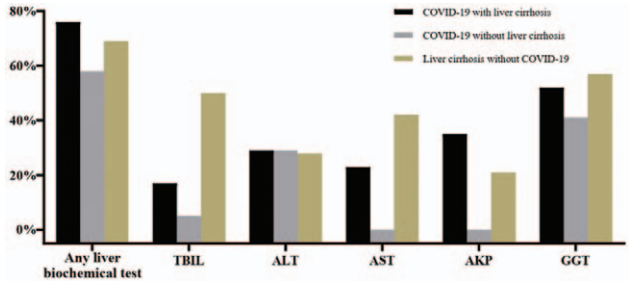

Figure 2. The incidence of liver biochemical abnormality in COVID-19 patients with and without liver cirrhosis and liver cirrhosis patients without COVID-19 at admission.

logical treatment, but not endoscopy. Medical treatments of COVID-19 were summarized in Table 2, including traditional Chinese medicine, antiviral drugs, antibiotics, systemic corticosteroids, and intravenous immunoglobulin. As for antiviral drugs, 4, 3, and 1 patient received arbidol, interferon alfa-2b, and oseltamivir, respectively. As for antibiotics, 3, 2, 1, and 1 patient received moxifloxacin, piperacillin-tazobactam, metronidazole, and levofloxacin, respectively. One patient was injected with convalescent plasma.

Only one patient with gastrointestinal bleeding and ascites had been transferred to ICU for 4 days. All patients were cured and discharged.

3.4. COVID-19 with versus without liver cirrhosis

COVID-19 patients with liver cirrhosis had significantly higher levels of TBIL, AST, AKP, AST/ALT, PT, INR, and APTT at admission ($P=.010$, .009, .004, .007, .015, .015, and .015, respectively), but significantly lower levels of HB and PLT ($P=.012$ and $<.001$, respectively) than those without liver cirrhosis (Table 1). However, there was no significant difference in the prevalence of respiratory symptoms and levels of ALB, ALT, GGT, WBC, CRP, lymphocyte count and percentage, neutrophil count and percentage, and choices of medical treatments between the two groups.

The incidence of liver biochemical abnormality at admission was 76.50% (13/17) and 58.80% (10/17) in COVID-19 patients with and without liver cirrhosis, respectively ($P=.271$). Elevated AST (23.50% versus 0.00%, $P=.033$) and AKP (35.30% versus 0.00%, $P=.007$) were significantly more common in COVID-19 patients with liver cirrhosis than those without liver cirrhosis (Fig. 2). Then, all the COVID-19 patients were divided into moderate and severe groups. In the moderate group, the incidence of liver biochemical abnormality at admission was 88.90% (8/9) and 44.40% (4/9) in COVID-19 patients with and without liver cirrhosis, respectively ($P=.046$); in the severe group, the incidence of liver biochemical abnormality at admission was 75.00% (6/8) and 62.50% (5/8) in COVID-19 patients with and without liver cirrhosis, respectively ($P=.590$).

Among the 28 patients in whom liver biochemistry was re-tested, the incidence of liver biochemical abnormality during hospitalizations was 84.60% (11/13) and 60.00% (9/15) in COVID-19 patients with and without liver cirrhosis, respectively ($P=.150$). The peak ALT level during hospitalizations was significantly higher in COVID-19 patients with liver cirrhosis than those without liver cirrhosis. There was no significant difference in liver biochemical indicators detected before discharge (Table 3).

There was no significant difference in the length of hospitalization between the two groups (15.29 ± 10.37 versus 21.18 ± 7.03, $P=.051$). Similarly, none of the COVID-19 patients without liver cirrhosis were transferred to the ICU or died during hospitalization.

3.5. Liver cirrhosis with versus without COVID-19

Liver cirrhosis patients with COVID-19 had significantly higher prevalence of respiratory symptoms and level of ALB at admission ($P=.030$), but significantly lower prevalence of gastrointestinal bleeding ($P=.020$) and fatigue ($P=.001$) and level of APTT ($P=.003$) and less decompensated events at admission ($P=.036$) than those without COVID-19 (Table 1). However, there was no significant difference in liver biochemical indicators, blood routine examinations, and Child-Pugh and MELD scores between the two groups. All liver cirrhosis patients without COVID-19 who were admitted to the hospital during the same period due to complications related to liver cirrhosis, and 5 of them underwent endoscopic variceal band ligation.

Table 2

Difference of medical treatment strategy during hospitalization between COVID-19 with liver cirrhosis versus COVID-19 without liver cirrhosis and liver cirrhosis without COVID-19.

Variables	No. Pts	COVID-19 with liver cirrhosis	No. Pts	COVID-19 without liver cirrhosis	No. Pts	Liver cirrhosis without COVID-19	$P^{\#}$ value	P^{*} value
Antivirals (%)	17	10 (58.80%)	17	10 (58.80%)	14	NA	1.000	NA
Antibiotics (%)	17	7 (41.20%)	17	7 (41.20%)	14	NA	1.000	NA
Intravenous Immunoglobulin (%)	17	1 (5.90%)	17	4 (23.50%)	14	NA	0.146	NA
Traditional Chinese Medicine (%)	17	11 (64.70%)	17	15 (88.20%)	14	NA	0.106	NA
Systemic Corticosteroids (%)	17	1 (5.90%)	17	5 (29.40%)	14	NA	0.072	NA

$P^{\#}$: Comparison between COVID-19 with and without liver cirrhosis; P^{*}: Comparison between liver cirrhosis with and without COVID-19.

Table 3

Difference of liver biochemical tests during hospitalization between COVID-19 with liver cirrhosis versus COVID-19 without liver cirrhosis and liver cirrhosis without COVID-19.

Variables	No. Pts	COVID-19 with liver cirrhosis	No. Pts	COVID-19 without liver cirrhosis	No. Pts	Liver cirrhosis without COVID-19	$P^{\#}$ value	P^{*} value
Peak Liver Biochemical Tests during Hospitalization								
Total Bilirubin (μmol/L)	9	22.00 (6.70–56.10) 23.54 ± 16.47	13	12.10 (5.50–30.00) 13.60 ± 7.80	8	30.70 (15.80–35.20) 27.59 ± 7.50	.217	.178
Alanine Aminotransferase (U/L)	9	30.00 (7.80–260.20) 56.09 ± 78.53	13	28.00 (8.90–58.40) 29.36 ± 16.07	8	21.85 (7.29–100.26) 35.46 ± 31.09	*.005*	.336
Aspartate Aminotransferase (U/L)	9	37.60 (12.90–280.3) 59.89 ± 83.28	13	18.10 (12.10–34.70) 19.82 ± 6.91	8	43.09 (26.41–187.07) 69.45 ± 55.92	.764	.441
Alkaline Phosphatase (U/L)	9	87.60 (49.80–309.10) 126.49 ± 85.54	13	74.30 (36.00–116.90) 75.46 ± 22.54	8	100.68 (49.09–372.64) 147.65 ± 116.62	.089	.700
Gamma-Glutamyl Transpeptidase (U/L)	9	64.80 (16.90–505.70) 100.92 ± 154.52	13	34.40 (12.70–139.30) 43.09 ± 39.03	8	85.93 (15.73–1298.04) 265.38 ± 437.88	.243	.386
Liver Biochemical Tests before Discharge								
Total Bilirubin (μmol/L)	13	18.60 (5.50–46.40) 20.65 ± 14.05	11	9.20 (4.10–38.90) 13.01 ± 9.60	9	22.80 (16.70–58.50) 32.14 ± 15.52	.207	.117
Alanine Aminotransferase (U/L)	13	30.70 (8.80–182.00) 38.08 ± 44.43	11	33.90 (11.80–101.80) 41.80 ± 29.63	9	22.36 (5.79–158.34) 40.80 ± 50.89	.111	.616
Aspartate Aminotransferase (U/L)	13	29.70 (15.10–201.00) 47.35 ± 50.23	11	20.70 (13.30–67.40) 25.77 ± 15.40	9	30.62 (18.41–162.02) 54.69 ± 51.85	.543	.367
Alkaline Phosphatase (U/L)	13	78.10 (64.10–379.60) 115.08 ± 85.15	11	75.90 (30.80–744.30) 131.89 ± 204.11	9	96.57 (47.50–241.26) 104.80 ± 59.76	.339	.764
Gamma-Glutamyl Transpeptidase (U/L)	13	38.80 (11.20–537.50) 93.88 ± 137.63	11	45.00 (19.80–74.10) 46.67 ± 20.09	9	66.40 (16.45–544.53) 118.83 ± 164.51	.505	.404
Liver Biochemical Abnormality during Hospitalization (%)	13	11 (84.60%)	15	9 (60.00%)	11	9 (81.80%)	.150	.855

$P^{\#}$: Comparison between COVID-19 with and without liver cirrhosis; P^{*}: Comparison between liver cirrhosis with and without COVID-19.

The incidence of liver biochemical abnormality at admission was 76.50% (13/17) and 69.20% (9/14) in liver cirrhosis patients with and without COVID-19, respectively ($P = .657$) (Fig. 2). Among the 24 patients in whom liver biochemistry were re-tested, the incidence of liver biochemical abnormality during hospitalizations was 84.60% (11/13) and 81.80% (9/11) in liver cirrhosis patients with and without COVID-19, respectively ($P = .855$). There was no significant difference in peak levels of liver biochemical indicators during hospitalizations or levels of liver biochemical indicators detected before discharge (Table 3).

There was no significant difference in the length of hospitalization between the two groups (15.29 ± 10.37 versus 10.93 ± 7.34, $P = .334$). None of the liver cirrhosis patients without COVID-19 were transferred to the ICU or died during hospitalization.

4. Discussion

The present study focused on the incidence of liver biochemical abnormality among COVID-19 patients with and without liver cirrhosis. The incidence of liver biochemical abnormality in our COVID-19 patients without liver cirrhosis was 58.80%. Similarly, previous studies have shown that the incidence of liver injury in patients with SARS-CoV-2 infection ranges from 14.8% to 53%,[14] and the incidence of elevated ALT and AST are 2.5%–50.0% and 2.5%–61.1%, respectively.[15] By comparison, COVID-19 patients with liver cirrhosis had worse liver and coagulation functions than those without. This is consistent with the findings of our previous meta-analysis that COVID-19 patients with liver diseases may be more prone to have abnormal liver biochemical indicators.[16] Our study also found that the AST/ALT ratio, which is associated with progressive liver impairment in patients with chronic liver diseases[17] and high mortality in COVID-19 patients with liver cirrhosis,[7] was significantly higher in COVID-19 patients with liver cirrhosis than those without. This liver biochemical indicator may play a more important role in evaluating the disease severity in COVID-19 patients with liver cirrhosis.

The underlying mechanism of liver injury in COVID-19 patients with cirrhosis remains unclear. Except for the impact of liver cirrhosis itself on liver dysfunction, the most possible cause is that the liver is affected by severe inflammation secondary to viral infection.[18] Because the receptor of this virus, angiotensin converting enzyme 2 (ACE2), is expressed in liver and bile duct cells, SARS-CoV-2 may directly infect liver cells[19] and bind to ACE2-positive cholangiocytes to influence liver function.[20] Another potential cause is immune-mediated inflammation, especially inflammatory cytokine storm.[4] In addition, drugs related side effects can also lead to liver injury.[4] There are some reports regarding liver injury after taking oseltamivir[21] and intravenous methylprednisolone.[22] In our study, a significant proportion of COVID-19 patients are also treated with antibiotics, antivirals, and corticosteroids which may exacerbate liver injury.

Additionally, as compared to those without COVID-19, cirrhotic patients with COVID-19 have lower Child-Pugh score and incidence of liver complications. This finding seems to be counter-intuitive, but can be explained by the characteristics of patients included. During the COVID-19 pandemic, our cirrhotic patients with COVID-19 were admitted due to SARS-CoV-2 infection more than liver cirrhosis. By contrast, our cirrhotic patients without COVID-19 who were admitted during the same study period had more severe complications secondary to liver cirrhosis and required urgent management. Even though fragile

patients, such as those with liver cirrhosis, may be infected with COVID-19 during hospitalizations, they are often at a higher risk of death due to severe complications secondary to their underlying diseases and need hospital care in a timely fashion.[23] Therefore, the prevention and early treatment of complications of liver cirrhosis should not be ignored during COVID-19 pandemic[24] and formulate a reasonable management process to ensure that cirrhotic patients without COVID-19 could receive treatment.[25]

Liver cirrhosis should be considered a high-risk comorbidity. Global registry demonstrates that mortality is 33% in liver cirrhosis patients with COVID-19.[26] Inpatients with cirrhosis and COVID-19 have a higher mortality than those with COVID-19 alone.[27,28] Presence of liver cirrhosis should be an independent predictor of COVID-19 mortality (odds ratios = 12.5, $P = .009$).[29] A meta-analysis further shows an increased risk of severity and mortality in COVID-19 patients with liver diseases.[30] One possible explanation may be that the liver is enriched in lymphocytes, including T and B lymphocytes, and natural killer cells, and plays an important role in both adaptive and innate immune responses.[31] In our study, 47.1% of COVID-19 patients with liver cirrhosis were diagnosed as severe cases, and 41.2% developed new decompensation events, despite none dying.

Our study has some features. First, we include a control group with liver cirrhosis but without COVID-19 and a control group with COVID-19 without liver cirrhosis to explore the characteristics of COVID-19 patients with liver cirrhosis. Second, all patients are hospitalized during the same period and receive similar treatment strategies, which can balance some confounding factors associated with the patients' outcomes. Our study also has some limitations. First, there are a relatively small number of COVID-19 patients with liver cirrhosis without death, which restricts further analysis of predictive factors for in-hospital outcome. Second, the study population was from China. Our findings may not be generalizable to the patients living in other parts of the world.

In conclusion, liver biochemical abnormality is more common in COVID-19 patients with liver cirrhosis. However, liver cirrhosis patients without COVID-19 have more hepatic decompensation events, so they should not be delayed from their hospitalization management during the COVID-19 pandemic. Further well-designed large-scale studies should be necessary to validate these findings and establish the strategy for managing patients with SARS-CoV-2 infection and liver cirrhosis.

Acknowledgments

We are indebted to all the medical staff who volunteered to participate in the treatment of COVID-19 patients at the Wuhan Huoshenshan Hospital.

Author contributions

Conceptualization: Xingshun Qi.
Data curation: Yang An, Zhuang Ma, Yufu Tang, Hao Meng, Hao Yu, Chengfei Peng, Guiyang Chu, Xinwei Wang, Yue Teng, Quanyu Zhang, Tianyi Zhu, Bing Wang, Zhenhua Tong, Xingshun Qi.
Formal analysis: Yang An, Xingshun Qi.
Investigation: Yang An, Zhuang Ma, Xiaozhong Guo, Yufu Tang, Hao Meng, Hao Yu, Chengfei Peng, Guiyang Chu, Xinwei Wang, Yue Teng, Quanyu Zhang, Tianyi Zhu, Bing Wang, Zhenhua Tong, Haitao Zhao, Hui Lu, Xingshun Qi.
Methodology: Yang An, Xingshun Qi.
Project administration: Zhuang Ma, Hui Lu, Xingshun Qi.
Supervision: Hui Lu, Xingshun Qi.
Writing – original draft: Yang An, Xingshun Qi.
Writing – review and editing: Yang An, Zhuang Ma, Xiaozhong Guo, Yufu Tang, Hao Meng, Hao Yu, Chengfei Peng, Guiyang Chu, Xinwei Wang, Yue Teng, Quanyu Zhang, Tianyi Zhu, Bing Wang, Zhenhua Tong, Haitao Zhao, Hui Lu, Xingshun Qi.

References

[1] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 2020;395:1054–62.
[2] https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed February 23, 2021.
[3] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. NEJM 2020;382:1708–20.
[4] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–30.
[5] Qi X, Liu Y, Wang J, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. Gut 2020.
[6] Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 Among patients with preexisting liver disease in the United States: a multicenter research network study. Gastroenterology 2020.
[7] Sarin SK, Choudhury A, Lau GK, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). Hepatol Int 2020;14:690–700.
[8] Gacouin A, Locufier M, Uhel F, et al. Liver cirrhosis is independently associated with 90-day mortality in ARDS patients. Shock 2016; 45:16–21.
[9] Shalimar , Elhence A, Vaishnav M, et al. Poor outcomes in patients with cirrhosis and Corona virus disease-19. Indian J Gastroenterol 2020;1–7.
[10] Qi X, Wang J, Li X, et al. Clinical course of COVID-19 in patients with pre-existing decompensated cirrhosis: initial report from China. Hepatol Int 14 2020;478–82.
[11] Peng Y, Qi X, Dai J, et al. Child-Pugh versus MELD score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis. Int J Clin Exp Med 2015;8:751–7.
[12] General Office of National Health Commission of the People's Republic of China OoNAoTCM. Diagnosis and treatment of corona virus disease-19 (7th trial edition). China Med 2020;15:801–5.
[13] Hong KH, Lee SW. Guidelines for laboratory diagnosis of Coronavirus disease 2019 (COVID-19) in Korea. Ann Lab Med 2020;40:351–60.
[14] Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998–1004.
[15] Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease-what we know on 1st May 2020. Aliment Pharmacol Ther 2020;52:267–75.
[16] Wu Y, Li H, Guo X, et al. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. Hepatol Int 2020;1–17.
[17] Nyblom H, Björnsson E, Simrén M, et al. The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver Int 2006; 26:840–5.
[18] Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol 2020;8:13–7.
[19] Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol 2003; 200:282–9.
[20] Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Biorxiv 2020;02:
[21] Fang S, Qi L, Zhou N, et al. Case report on alimentary tract hemorrhage and liver injury after therapy with oseltamivir: a case report. Medicine 2018;97:e12497.
[22] Cottin J, Pierre S, Pizzoglio V, et al. Methylprednisolone-related liver injury: a descriptive study using the French pharmacovigilance database. Clin Res Hepatol Gastroenterol 2020.

[23] Lleo A, Invernizzi P, Lohse AW, et al. Management of patients with autoimmune liver disease during COVID-19 pandemic. J Hepatol 2020; 73:453–5.
[24] Viganò M, Carbone M. Let's not forget our COVID-19-free cirrhotic patients!. Liver Int 2020;40:1508–9.
[25] Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. Hepatol Int 2020;14: 415–28.
[26] SECURE Cirrhosis Registry. Updates and data. Available at: https://covid cirrhosis.web.unc.edu/updat es-and-data/. Accessed August 30, 2020.
[27] Bajaj JS, Garcia-Tsao G, Biggins SW, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. Gut 2020.
[28] Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020.
[29] Hashemi N, Viveiros K, Redd WD, et al. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: a multicentre United States experience. Liver Int 2020.
[30] Oyelade T, Alqahtani J. Prognosis of COVID-19 in patients with liver and kidney diseases: an early systematic review and meta-analysis. Trop Med Infect Dis 2020;5:
[31] Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385–96.