Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study

COVID-19 has rapidly become a global challenge.[1] We read with interest the article by Bezzio *et al*[1] that reported the characteristics and outcomes of COVID-19 patients with pre-existing IBD. Patients with pre-existing cirrhosis, who have immune dysfunction and poorer outcomes from acute respiratory distress syndrome (ARDS) than patients without cirrhosis, are also considered a high-risk population for COVID-19.[2 3] In previous studies, the proportion of COVID-19 patients with pre-existing liver conditions ranged from 2% to 11%.[2] However, the clinical course and risk factors for mortality in these patients has not yet been reported.

This retrospective multicentre study (COVID-Cirrhosis-CHESS, ClinicalTrials.gov NCT04329559) included consecutive adult patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and pre-existing cirrhosis from 16 designated hospitals in China between 31 December 2019 and 24 March 2020. Patient characteristics are summarised in table 1. Twenty-one COVID-19 patients with pre-existing cirrhosis (Child-Pugh class A, B and C in 16, 3 and 2 patients, respectively) were included in the analysis. The median age was 68 years; 11 (52.4%) were male. Most patients had compensated cirrhosis (81.0%) and chronic HBV infection was the most common aetiology (57.1%). Comorbidities other than cirrhosis were present in most patients (66.7%). In previous studies, older age, male sex and pre-existing comorbidities were associated with higher risk of mortality for COVID-19.[4 5] Here, there were no significant differences between survivors (n=16) and non-survivors (n=5) in age, sex, comorbidities, aetiology of cirrhosis, stage of cirrhosis, Child-Pugh class, Model for End-stage Liver Disease (MELD) score, interval between onset and admission, or onset symptoms of COVID-19. Comorbidities have been associated with adverse outcomes in cirrhosis,[6] but our analysis did not show clear prognostic associations—possibly due to the small size and narrow composition of the study population.

Fever and cough were the most common symptoms on admission, similar to previous studies of COVID-19 among general populations.[7 8] Elevations in aspartate transaminase, alanine aminotransferase and gamma-glutamyl transferase levels were present in 8 (38.1%), 5 (23.8%) and 5 (23.8%) patients, respectively. Leucopenia, lymphopenia and thrombocytopenia occurred in 8 (38.3%), 15 (71.4%) and 8 (38.1%) patients, respectively. Although abnormal haematological indices and portal hypertension are common in cirrhosis, patients with COVID-19 who died had lower total lymphocyte and platelet counts, and also higher direct bilirubin levels than patients who survived (p=0.040, 0.032 and 0.006, respectively). These findings are consistent with previous studies in the general COVID-19 population.[9 10]

Treatment and complications occurring during hospitalisation are summarised in table 2. The frequency of ARDS and GI bleeding were higher in non-survivors than survivors (100.0% vs 6.3%, p<0.001, and 60.0% vs 6.3%, p=0.028, respectively). Of the five non-survivors, all patients developed ARDS and two patients progressed to multiple organ dysfunction syndrome. One patient who died developed clear evidence of acute-on-chronic liver failure.

In contrast to Western populations, the main cirrhosis aetiology in this China-based study was chronic HBV, so it is unclear if our findings are generalisable to other geographic regions. To further define the clinical course of COVID-19 patients with pre-existing cirrhosis and confirm risk factors for mortality, larger prospective studies comprising patients with different cirrhosis aetiologies are expected.

In conclusion, we provide the first report of the demographic characteristics, comorbidities, laboratory and radiographic findings, and clinical outcomes in SARS-CoV-2-infected patients with pre-existing cirrhosis. The cause of death in most patients was respiratory failure rather than progression of liver disease (ie, development of acute-on-chronic liver failure). Lower lymphocyte and platelet counts, and higher direct bilirubin level might represent poor prognostic indicators in this patient population.

Xiaolong Qi,[1] **Yanna Liu**,[1] **Jitao Wang**,[2] **Jonathan A Fallowfield**,[3] **Jianwen Wang**,[4] **Xinyu Li**,[5] **Jindong Shi**,[6] **Hongqiu Pan**,[7] **Shengqiang Zou**,[7] **Hongguang Zhang**,[7] **Zhenhuai Chen**,[8] **Fujian Li**,[8] **Yan Luo**,[9] **Mei Mei**,[9] **Huiling Liu**,[9] **Zhengyan Wang**,[10] **Jinlin Li**,[10] **Hua Yang**,[11] **Huihua Xiang**,[12] **Xiaodan Li**,[13] **Tao Liu**,[14] **Ming-Hua Zheng**,[15] **Chuan Liu**,[1] **Yifei Huang**,[1] **Dan Xu**,[1] **Xiaoguo Li**,[1] **Ning Kang**,[1] **Qing He**,[16] **Ye Gu**,[17] **Guo Zhang**,[18] **Chuxiao Shao**,[19] **Dengxiang Liu**,[2] **Lin Zhang**,[20] **Xun Li**,[21] **Norifumi Kawada**,[22] **Zicheng Jiang**,[23]

Table 1 Clinical, laboratory and radiographic findings on admission

	Total (n=21)	Non-survivor (n=5)	Survivor (n=16)	P value
Clinical characteristics				
Age, years	68 (52–75)	68 (50–75)	69 (52–75)	0.842
Sex				0.311
Male	11 (52.4%)	4 (80.0%)	7 (43.8%)	–
Aetiology of cirrhosis				0.489
Chronic hepatitis B	9 (42.9%)	2 (40.0%)	7 (43.8%)	–
Chronic hepatitis C	2 (9.5%)	0 (0.0%)	2 (12.5%)	–
Alcoholic liver disease	2 (9.5%)	1 (20.0%)	1 (6.2%)	–
Schistosomiasis	1 (4.8%)	1 (20.0%)	0 (0%)	
Autoimmune hepatitis	1 (4.8%)	0 (0.0%)	1 (6.2%)	
Other*	6 (28.6%)	1 (20.0%)	4 (25.0%)	–
Stage of cirrhosis				0.228
Decompensated	4 (19.0%)	2 (40.0%)	2 (12.5%)	–
Child-Pugh class				0.354
A	16 (76.2%)	3 (60.0%)	13 (81.3%)	–
B	3 (14.3%)	0 (0.0%)	3 (18.8%)	–
C	2 (9.5%)	2 (40.0%)	0 (0.0%)	–
MELD score	8 (7–11)	11 (7–14)	8 (7–9)	0.398
Exposure history	20 (95.2%)	5 (100.0%)	15 (93.8%)	1.000
Interval between onset and admission, days	8 (3–14)	3 (3–20)	8 (4–15)	0.495
Onset symptoms				
Fever	16 (76.2%)	5 (100.0%)	11 (68.8%)	0.278
Cough	15 (71.4%)	4 (80.0%)	11 (68.8%)	1.000
Shortness of breath	12 (57.1%)	3 (60.0%)	9 (56.3%)	1.000
Sputum	7 (33.3%)	2 (40.0%)	5 (31.3%)	1.000
Sore throat	3 (14.3%)	0 (0.0%)	3 (18.8%)	0.549
Diarrhoea	2 (9.5%)	1 (20.0%)	1 (6.3%)	0.429
Comorbidities				
Any	13 (61.9%)	5 (100.0%)	8 (50.0%)	0.111
Hypertension	7 (33.3%)	2 (40.0%)	5 (31.3%)	1.000
Diabetes	4 (19.0%)	2 (40.0%)	2 (12.5%)	0.228
Coronary heart disease	4 (19.0%)	2 (40.0%)	2 (12.5%)	0.228
Chronic kidney disease	2 (9.5%)	0 (0.0%)	2 (12.5%)	1.000
Malignancy	3 (14.3%)	1 (20.0%)	2 (12.5%)	1.000
Laboratory characteristics				
White cell, $\times10^9$/L	4.34 (2.81–5.52)	4.60 (1.86–9.05)	4.28 (3.10–5.15)	0.905
Neutrophils, $\times10^9$/L	2.64 (1.68–4.30)	4.01 (1.54–7.45)	2.48 (1.64–4.22)	0.548
Lymphocytes, $\times10^9$/L	0.78 (0.51–1.24)	0.36 (0.20–1.10)	0.86 (0.70–1.29)	**0.040***
Platelets, $\times10^9$/L	120 (70–182)	77 (44–93)	126 (83–201)	**0.032***
ALT, U/L	30 (19–41)	30 (22–52)	28 (17–38)	0.603
AST, U/L	38 (27–55)	42 (32–105)	31 (26–51)	0.275
GGT, U/L	23 (20–59)	61 (22–151)	22 (17–27)	0.098
Total bilirubin, µmol/L	14.5 (10.60–22.50)	22.2 (16.60–34.60)	12.6 (8.90–20.00)	0.075
Direct bilirubin, µmol/L	4.8 (2.50–10.90)	12.0 (9.40–14.60)	3.90 (2.23–6.90)	**0.006***
Albumin, g/L	34.2 (26.90–38.60)	29.0 (22.30–36.00)	37.5 (27.60–38.70)	0.354
LDH, U/L	306 (238–429)	409 (178–573)	289 (234–344)	0.179
BUN, mmol/L	5.50 (3.97–7.65)	5.50 (3.98–10.40)	5.30 (3.85–7.10)	0.660
SCr, µmol/L	66.0 (48.70–90.40)	66.2 (59.30–94.50)	60.1 (47.20–87.90)	0.398
Glucose, mmol/L	6.20 (5.10–7.91)	7.90 (5.65–14.15)	6.06 (4.95–7.60)	0.208
Creatine kinase, U/L	87 (52–135)	63 (46–416)	91 (50–131)	0.968
APTT, s	29.1 (22.70–32.90)	32.9 (30.00–46.50)	28.1 (22.10–32.60)	0.075
Prothrombin time, s	12.8 (11.80–14.60)	14.0 (11.70–17.50)	12.6 (11.60–14.40)	0.445
INR	1.08 (1.00–1.30)	1.31 (1.00–1.59)	1.08 (0.99–1.17)	0.275
C-reactive protein, mg/L	18.30 (1.88–73.71)	50.00 (13.91–116.40)	7.20 (1.50–56.13)	0.153
Procalcitonin, ng/mL	0.05 (0.00–0.35)	0.10 (0.05–1.19)	0.04 (0.00–0.09)	0.130
CT evidence of pneumonia				
Typical signs of SARS-CoV-2 infection	18 (85.7%)	4 (80.0%)	14 (87.5%)	1.000

Data are expressed as median (IQR) or n (%). P values were calculated by Mann-Whitney U test or Fisher's exact test, as appropriate.
*Other: one for with HBV and HCV co-infection, one for hepatitis B infection with history of alcohol abuse, one for hepatitis B infection with schistosomiasis and three for unknown causes of cirrhosis.
ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyl transpeptidase; INR, international normalised ratio; LDH, lactate dehydrogenase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCr, serum creatinine.

Table 2 Treatment, complications and outcomes

	Total (n=21)	Non-survivor (n=5)	Survivor (n=16)	P value
Treatment				
ICU admission	5 (23.8%)	4 (80.0%)	1 (6.3%)	**0.004***
Antiviral treatment	17 (81.0%)	4 (80.0%)	13 (81.3%)	1.000
Antibiotic treatment	15 (71.4%)	5 (100.0%)	10 (62.5%)	0.262
Glucocorticoids	8 (38.1%)	5 (100.0%)	3 (18.8%)	**0.003***
Intravenous immunoglobulin	5 (23.8%)	3 (60.0%)	2 (12.5%)	0.063
Non-invasive ventilation	4 (19.0%)	3 (60.0%)	1 (6.3%)	**0.028***
Invasive mechanical ventilation	3 (14.3%)	3 (60.0%)	0 (0.0%)	**0.008***
CRRT	2 (9.5%)	2 (40.0%)	0 (0.0%)	**0.048***
ECMO	2 (9.5%)	2 (40.0%)	0 (0.0%)	**0.048***
Complications during hospitalisation				
Secondary infection	6 (28.6%)	3 (60.0%)	3 (18.8%)	0.115
Ascites	5 (23.8%)	2 (40.0%)	3 (18.8%)	0.553
Upper GI bleeding	4 (19.0%)	3 (60.0%)	1 (6.3%)	**0.028***
Acute-on-chronic liver failure	1 (4.8%)	1 (20.0%)	0 (0.0%)	0.238
Acute kidney injury	1 (4.8%)	1 (20.0%)	0 (0.0%)	0.238
Septic shock	3 (14.3%)	2 (40.0%)	1 (6.3%)	0.128
ARDS	6 (28.6%)	5 (100.0%)	1 (6.3%)	**<0.001***
Length of stay, days	16 (11–32)	16 (7–39)	16 (11–31)	0.842

One patient died in the emergency department without intensive care. Data are expressed as median (IQR) or n (%). P values were calculated by Mann-Whitney U test or Fisher's exact test, as appropriate.
*A two-sided p-value of less than 0.05 was considered statistically significant.
ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Fengmei Wang,[24] Bin Xiong ,[25] Tetsuo Takehara,[26] Don C Rockey ,[27] for the COVID-Cirrhosis-CHESS Group

[1]CHESS Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China
[2]CHESS-COVID-19 Group, Xingtai People's Hospital, Xingtai, China
[3]Centre for Inflammation Research, University of Edinburgh MRC Centre for Inflammation Research, Edinburgh, UK
[4]Department of Tuberculosis and Respiratory, Wuhan Jinyintan Hospital, Wuhan, China
[5]Department of Infectious Disease, Shanghai Fifth People's Hospital of Fudan University, Shanghai, China
[6]Department of Respiratory Medicine, Shanghai Fifth People's Hospital of Fudan University, Shanghai, China
[7]Department of Infectious Diseases and Critical Care Medicine, The Affiliated Third Hospital of Jiangsu University, Zhenjiang, China
[8]Department of Respiratory Medicine, The People's Hospital of Baoding, Baoding, China
[9]Department of Gastroenterology, Tianjin Haihe Hospital, Tianjin, China
[10]Department of Respiratory Medicine, Suizhou Hospital, Hubei University of Medicine, Suizhou, China
[11]Department of Respiratory Medicine, Minda Hospital Affiliated to Hubei University for Nationalities, Enshi, China
[12]Department of Radiology, Minda Hospital Affiliated to Hubei University for Nationalities, Enshi, China
[13]Department of Infectious Disease, The Central Hospital of Enshi Tujia And Miao Autonomous Prefecture, Enshi, China
[14]Department of Infectious Disease, The Central Hospital of Lichuan, Enshi, China
[15]MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[16]CHESS-COVID-19 Group, The Third People's Hospital of Shenzhen, Shenzhen, China
[17]CHESS-COVID-19 Group, The Sixth People's Hospital of Shenyang, Shenyang, China
[18]CHESS-COVID-19 Group, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China
[19]CHESS-COVID-19 Group, Zhejiang University Lishui Hospital and Lishui Central Hospital, Lishui, China
[20]Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China
[21]The First Hospital of Lanzhou University, Lanzhou, China
[22]Department of Hepatology, Graduate School of Medicine, Osaka City University, Osaka, Japan
[23]Department of Infectious Disease, Ankang Central Hospital, Ankang, China
[24]Department of Gastroenterology and Hepatology, Tianjin Second People's Hospital, Tianjin, China
[25]Department of Radiology, Wuhan Union Hospital, Wuhan, China
[26]Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, Japan
[27]Division of Gastroenterology and Hepatology, Medical University South Carolina, Charleston, South Carolina, USA

Correspondence to Professor Xiaolong Qi, CHESS Center, Institute of Portal Hypertension, Lanzhou University First Affiliated Hospital, Lanzhou 730000, China; qixiaolong@vip.163.com and Dr Bin Xiong, Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; herr_xiong@126.com

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ORCID iDs
Xiaolong Qi http://orcid.org/0000-0002-3559-5855
Jonathan A Fallowfield http://orcid.org/0000-0002-5741-1471
Ming-Hua Zheng http://orcid.org/0000-0003-4984-2631
Bin Xiong http://orcid.org/0000-0002-7795-7041
Don C Rockey http://orcid.org/0000-0002-3751-2961

REFERENCES

1 Bezzio C, Saibeni S, Variola A, *et al*. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020;69:1213–7.
2 Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5:428–30.
3 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.
4 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020. doi:10.1001/jama.2020.2648. [Epub ahead of print: 24 Feb 2020] (Epub ahead of print: 24 Feb 2020).
5 Onder G, Rezza G, Brusaferro S. Case-Fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 2020. doi:10.1001/jama.2020.4683. [Epub ahead of print: 23 Mar 2020].
6 Jepsen P, Vilstrup H, Andersen PK, *et al*. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. *Hepatology* 2008;48:214–20.
7 Guan WJ, ZY N, Hu Y, *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
8 Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020. doi:10.1001/jama.2020.1585. [Epub ahead of print: 07 Feb 2020].
9 Li L-Q, Huang T, Wang YQ, *et al*. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020.
10 Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020;506:145–8.