Severe Acute Respiratory Syndrome Coronavirus 2–related Acute-on-chronic Liver Failure

Dear Editor

Acute-on-chronic liver failure (ACLF) is a condition associated with hepatic and extrahepatic organ failure with high short-term mortality.[2] The data regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related ACLF (S-ACLF) are scarce.[2–8] Whether patients with cirrhosis are at a high risk of developing ACLF after coronavirus disease 2019 (COVID-19) needs further elucidation. Here, we report our observation of patients with COVID-19 and ACLF (as per European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) definition).[2] We prospectively collected the clinical and laboratory data between 1st June and 10th October of 2020. Fifty seven (2.3%) of 2460 patients with COVID-19 had underlying cirrhosis, and 60% of patients had cirrhosis-related symptoms at presentation. The clinical and laboratory data are described in Table 1. Patients with S-ACLF (35%) had significantly prolonged hospital stay (14.7 ±17.3 days vs. 5.4 ±5.3 days, p-0.004), severe COVID-19 illness (25% vs. 3%, p-0.03), need for intensive care unit (45% vs. 11%, p-0.003), and higher mortality (30% vs. 5%, p-0.01) as compared with patients without ACLF. The cause of death was respiratory failure in 5 (67%) and liver failure in 3 (37%) patients. There were no differences in laboratory parameters between those who died and survived in the S-ACLF group. Patients who died had significantly higher Chronic Liver Failure Consortium (CLIF C) score (56.8 ±4.8 vs.43.3 ±6.4, p-<0.001), CLIF C organ failure score (12.1 ±1.4 vs.9.7 ±1.6,p-0.005), and ACLF grade (3.1 ±0.9 vs.1.9 ±0.6,p-0.003).

Patients with ACLF are more prone to develop severe COVID-19 illness because of profound immune dysregulation.[1] It is unclear whether outcomes in S-ACLF will be different compared with the other causes of ACLF. Our cohort demonstrated lower mortality in patients with cirrhosis, contrary to other studies despite having similar disease severity. Our cohort's better outcomes could be due to prompt usage of steroids in patients with moderate or severe COVID-19.[4–8] The patients tolerated steroids well, and four patients developed gram-negative sepsis,

Table 1 Comparison of Patients with S-ACLF and Patients with COVID-19 and without ACLF.

Parameters	S-ACLF (n-20)	Non-ACLF (n-37)	*P* value
Age (years)	48.4 ± 10.9	53 ± 12.3	0.174
Male (n, %)	19 (95)	32 (86)	0.318
Comorbidities (n, %)			
Diabetes mellitus	2 (10)	19 (51)	**0.002**
Hypertension	2 (10)	12 (32)	0.060
Coronary artery disease	1 (5)	3 (8)	0.661
Etiology of cirrhosis (n, %)			
Alcohol	13 (65)	12 (32.4)	0.094
Cryptogenic	3 (15)	6 (16.2)	
Nonalcoholic steatohepatitis	1 (5)	12 (32.4)	
Viral	2 (10)	5 (13.5)	
Autoimmune	1 (5)	2 (5.5)	
Compensated cirrhosis[a] (n, %)	10 (50)	20 (54)	0.770
Severity of cirrhosis			
Child Pugh score, A/B/C (%)	11 ± 1.7, 0/25/75	8 ± 2.4,29.7/40.6/29.7	**<0.001**
Sodium MELD	28.4 ± 7.5	15.2 ± 8.7	**<0.001**

(*Continued*)

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Table 1. Comparison of Patients with S-ACLF and Patients with COVID-19 and without ACLF. (*Continued*)

Parameters	S-ACLF (n-20)	Non-ACLF (n-37)	*P* value
Acute hepatic decompensation (%)			
Ascites/hepatic encephalopathy/variceal bleed	70/50/5	40/8/2	**0.002/<0.001**/0.065
ACLF severity scores			
CLIF C ACLF score	48 ± 8.6		
ACLF CLIF C organ failure score	10 ± 1.9		
ACLF grade – 1/2/3 (%)	15/50/35		
COVID-19 severity grade (%)			
Mild (no hypoxia)/moderate (SpO2 90–94%)/severe (SpO2<90%) on room air	45/30/25	54/33/3	**0.030**
Laboratory parameters			
Hemoglobin (g/dL)	9.1 ± 1.8	10.4 ± 2.2	**0.031**
Total leukocyte count/μL	9.9 ± 9.2	6 ± 3.7	**0.028**
Lymphocytopenia, <1000/μL (n, %)	4 (20)	18 (48.6)	**0.034**
Platelets/μL[a]10^3	1.1 ± 0.4	1.2 ± 0.8	0.756
Sodium (meq/l)	130.8 ± 5.6	132.8 ± 4.8	0.169
Creatinine (mg/dl)	1.5 ± 1	1 ± 0.3	**0.003**
Total/direct bilirubin(mg/dL)	14.9 ± 10.6/7.6 ± 6.6	2.9 ± 2.4/1.3 ± 1.5	**<0.001**
Aspartate transaminase (<40 U/L)	173 ± 204	109 ± 171	0.212
Alanine transaminase (<40 U/L)	73.6 ± 77.8	57 ± 66.5	0.402
Alkaline phosphatase (30–120 U/L)	141.5 ± 65.2	114 ± 56.5	0.103
Total protein (g/dL)	6 ± 1	6.5 ± 0.7	**0.048**
Serum albumin (g/dL)	2.7 ± 0.4	3 ± 0.5	0.082
International normalized ratio	2.5 ± 1.3	1.5 ± 0.6	**<0.001**
Inflammatory biomarkers (reference range)			
Interleukin-6 (pg/ml, <7)	64.5 ± 97.6	49.5 ± 89	0.558
D-dimer (ng/ml, <232)	2534.4 ± 2019.7	1406.4 ± 1688	**0.029**
C-reactive protein (mg/l, <6)	17.8 ± 25.9	15.9 ± 27.6	0.809
Lactate dehydrogenase (U/L,225–450)	523.4 ± 463.5	405.4 ± 417.1	0.331
Ferritin(ng/ml,30–400)	906.6 ± 1262.5	560.7 ± 1227.2	0.319
Hospital admission (n, %)	16 (80)	22 (59)	0.116
Intensive care unit	9 (45)	4 (11)	**0.003**
Oxygen requirement	11 (55)	13 (65)	0.147
Mechanical ventilation	7 (35)	1 (2)	**0.001**
COVID-19 treatment			
Supportive	4 (20)	12 (32)	
Remdesivir	6 (30)	14 (38)	0.130
Doxycycline	10 (50)	11 (30)	0.554
Steroids	13 (65)	16 (43)	0.114
Length of hospital stay (days)	14.7 ± 17.3	5.4 ± 5.3	**0.004**
Mortality (n, %)	6 (30)	2 (5)	**0.011**

All results are expressed in mean ± standard deviation unless otherwise specified. ACLF, acute-on-chronic liver failure; MELD, Model for End-Stage Liver Disease; CLIF C, Chronic Liver Failure Consortium; COVID-19, coronavirus disease 2019; SpO2, oxygen saturation in pulse oximeter.

Bold describes the Significant values.

[a] Before the onset of COVID-19 illness.

which responded to broad-spectrum antibiotics. The exact mechanism of S-ACLF is unclear, and the cytokine storm might serve as a trigger in these patients. It is also hypothesized that direct SARS-CoV-2 infection can cause significant liver injury because of the upregulated Angiotensin converting enzyme 2 (ACE2) expression and higher ACE2 internalization in hepatocytes, causing worsening of liver fibrosis and portal hypertension to ACLF in decompensated cirrhosis.[9] In addition, a liver biopsy might have helped in better understanding of the cause and severity of S-ACLF. Excessive systemic inflammation is a hallmark in ACLF, and these patients had higher leukocyte count and elevated D-dimer in our study. The inflammatory response observed in our study is comparable with that of patients with COVID-19 without cirrhosis, as described in recent metanalysis.[10] Whether immune dysregulation in S-ACLF is different from ACLF of other causes and cirrhosis needs further evaluation. We speculate that the SARS-CoV-2 infection predominantly determines immune dysregulation and outcomes irrespective of cirrhosis severity. In conclusion, S-ACLF is associated with a poor outcome, and early recognition and aggressive treatment of COVID-19 is warranted. Further multicentre studies with a larger sample size will provide more robust data on S-ACLF outcomes.

COVID-19

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Pramod Kumar: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Mithun Sharma:** Reviewing and editing. **Syeda F. Sulthana:** Compilation. **Anand Kulkarni:** Reviewing and editing. **Padaki N. Rao:** Supervision. **Duvvuru N. Reddy:** Supervision.

CONFLICTS OF INTEREST

The authors have none to declare.

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Pramod Kumar, Mithun Sharma, Syeda F. Sulthana, Anand Kulkarni, Padaki N. Rao
Department of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology Hospitals, Hyderabad, IndiaDepartment of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology Hospitals, Hyderabad, India

Duvvuru N. Reddy
Department of Gastroenterology, Asian Institute of Gastroenterology Hospitals, Hyderabad, IndiaDepartment of Gastroenterology, Asian Institute of Gastroenterology Hospitals, Hyderabad, India

Address for correspondence: Dr. Pramod Kumar. MD., Department of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology Hospitals, Survey No 136, Mindspace Rd, Gachibowli, Hyderabad, Telangana 500032, India. Tel.: +91 9814933544.
E-mail: dapramod@gmail.com (P. Kumar)

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