Poor Outcomes in Patients with Cirrhosis and COVID-19

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Abstract

Background and Aim

There is a paucity of data on the clinical presentations and outcomes of Coronavirus disease 2019(COVID-19) in patients with underlying liver disease. We aimed to summarize the presentations and outcomes of COVID-19 positive patients and compare with historical controls.

Methods

Patients with known chronic liver disease who presented with superimposed COVID- 19(n=28) between 22nd April and 22nd June 2020 were studied. Seventy-eight cirrhotic patients from historical controls were taken as comparison group.

Results

A total of 28 COVID patients- two without cirrhosis, one with compensated cirrhosis, sixteen with acute decompensation (AD), and nine with acute-on-chronic liver failure(ACLF) were included. The etiology of cirrhosis was alcohol(n=9), non-alcoholic fatty liver disease(n=2), viral(n=5), autoimmune hepatitis(n=4), and cryptogenic cirrhosis(n=6). The clinical presentations included complications of cirrhosis in 12(46.2%), respiratory symptoms in 3(11.5%) and combined complications of cirrhosis and respiratory symptoms in 11(42.3%) patients. The median hospital stay was 8(7-12) days. The mortality rate in COVID-19 patients was 42.3%(11/26), as compared to 23.1%(18/78) in the historical controls(p=0.077). All COVID-19 patients with ACLF(9/9) died compared to 53.3%(16/30) in ACLF of historical controls(p=0.015). Mortality rate was higher in COVID patients with compensated cirrhosis and AD as compared to historical controls 2/17(11.8%) vs 2/48(4.2%), though not statistically significant (p=0.278). Requirement of mechanical ventilation independently predicted mortality (hazard ratio, 13.68). Both non-cirrhotic patients presented with respiratory symptoms and recovered uneventfully.

Conclusion

COVID-19 is associated with poor outcomes in patients with cirrhosis, with worst survival rates in ACLF. Mechanical ventilation is associated with a poor outcome.

Study Highlights

What is already known?

- COVID-19 has high a mortality in patients with comorbidities such as diabetes, hypertension and obesity.
- The effect and outcome of COVID-19 in patients with underlying cirrhosis is

What is new in this study?

- Patients with cirrhosis and COVID-19 have poor outcome as compared to those without COVID-19.
- The survival rates are worst amongst COVID patients with acute-on-chronic liver failure (ACLF).

What are the future clinical and research implications of the study findings?

- Future studies should assess the role of newer drugs in patients with

Introduction

Since 30th January 2020, when India reported its first case of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome- coronavirus 2 (SARS-CoV2), the total number of cases have increased to 4,40,462 as on 22nd June 2020 [1]. Although the COVID–19 disease predominantly presents as a respiratory illness in the majority of the patients, extrapulmonary manifestations also have been described [2]. The tropism of the virus to angiotensin-converting enzyme–2 (ACE–2) receptors [3] and its presence on the hepatic endothelial cells and cholangiocytes [4] may predispose to direct hepatotoxic injury [5].

Liver enzyme derangements are common, seen in 14 to 53% of COVID–19 cases [2]. The clinical consequences are not well known in patients without liver disease since the majority of these derangements are mild in nature and hence clinically inconsequential [6]. However, their impact on patients with underlying liver diseases is beginning to emerge. Evolving data from a global registry suggests a poor outcome in patients with cirrhosis. Among these, 45% presented with new decompensation, and the mortality rate was 33%. In contrast, 303 patients with chronic liver disease (CLD) without cirrhosis fared better with a mortality rate of 8% [7].

Genetic variability across the world can potentially impact the severity of SARS-CoV2 infection which account for a myriad of possible presentations and outcomes. However, there is a paucity of data on the presentations and outcomes of COVID–19 infected patients with underlying liver diseases from different part of the world. We report our experience of patients with liver disease and COVID–19.

Patients And Methods

Patient population

In this observation study, all consecutive patients with known liver disease presenting between 22nd April 2020 and 22th June 2020 were included. Patients were diagnosed as COVID–19 (RT-PCR positive for SARS-CoV–2) as per the Indian Council of Medical Research (ICMR) criteria [8]. Data was collected from a prospectively maintained database of all patients from admission until endpoint of the study (discharge or death or deadline of 22nd June 2020).

We compared the results of COVID positive patients with age, sex, and severity matched cirrhosis patients (historical controls) from previously published data from our center [9,10].

Patient evaluation and treatment

All consecutive patients with liver disease presenting to the emergency with either fever or respiratory symptoms or chest X-ray showing infiltrates were tested for COVID–19 as per the hospital policy. Patients who had no symptoms or tested negative initially were offered to retest based on the development of new respiratory symptoms or fever at the discretion of the treating physician. Nasal and throat swabs were taken and transported in a viral transport media (Hank's balanced salt solution) and tested by reverse transcriptase-polymerase chain reaction (RT-PCR). Patients with confirmed COVID–19 pneumonia were offered broad- spectrum antibiotics, hydroxychloroquine (HCQ) with or without ivermectin according to the evolving consensus [11]. Complications of liver disease including organ failures were managed according to the standard guidelines [12].

Definitions

Abnormalities in the liver function tests (LFT) were based on our hospital cut-offs- bilirubin (>1 mg/dl), aspartate aminotransferase (AST >40 IU/L), alanine aminotransferase (ALT >40 IU/L), and alkaline phosphatase (ALP >280 IU/L). Cirrhosis was defined by the presence of a nodular outline of liver on imaging and concomitant evidence of portal hypertension, such as a dilated portal vein, splenomegaly. Patients with cirrhosis who had a current history of variceal bleed, ascites, hepatic encephalopathy or jaundice were labelled as having Acute Decompensation (AD). Acute-on-chronic liver failure (ACLF) was defined according to the European Association of the study of the Liver (EASL)-chronic liver failure (CLIF) consortium definition- characterized by a hepatic or extrahepatic insult in a patient with underlying chronic liver disease and associated with prespecified organ failure [13]. The clinical presentations were defined as complications of cirrhosis as defined above and as respiratory when the presentation was predominantly with cough, breathlessness and pneumonia. The hospital stay was counted onwards from the date of COVID–19 detection for cases diagnosed during their hospitalization and from the date of admission for those who presented with a positive test. The clinical severity of COVID–19 was defined according to the Ministry of Health and Family Welfare (MOHFW) criteria as follows- mild disease as patients with only upper respiratory tract symptoms without any signs of breathlessness and hypoxia. Moderate severity was defined as the presence of pneumonia with the respiratory rate (RR) between 24–30/minute and SpO2 between 90–94% on room air while the severe disease was defined by the presence of pneumonia with RR >30/minute or SpO2 <90% on room air or severe respiratory distress [14].

Statistical analysis

Normally distributed data were expressed as mean ± standard deviation (SD), and skewed data were expressed as median with an interquartile range where applicable. Nominal data were expressed as frequency and percentage. Student's t-test or Mann-Whitney U test was used for comparing continuous data as appropriate. The Chi-square test or Fisher's exact test for categorical variables was used whenever applicable. Univariate and multivariate Cox- regression analysis was performed for analysis of

predictors of in-hospital mortality. A p- value of < 0.05 was considered significant. Data were analyzed using IBM SPSS statistical software (Version 20.0, Chicago, IL, USA).

Ethical clearance

In this retrospective analysis requirement of consent was waived off. The study was approved by the institutional ethics committee.

Results

Twenty-eight patients with underlying liver disease admitted with COVID–19 included 26 patients with liver cirrhosis and two without cirrhosis (one each with NAFLD and extrahepatic portal venous obstruction, EHPVO). Among patients with cirrhosis, one had compensated cirrhosis, 16 had AD, and 9 presented with ACLF. The median age of patients was 48 (38–58) years, and 20 (71.4%) were males. The etiology of cirrhosis was alcohol- related in 9 (34.6%), NAFLD in 2 (7.7 %), hepatitis B virus (HBV) in 3 (11.5%), hepatitis C virus (HCV) in 2 (7.7%), autoimmune hepatitis (AIH) in 4 (15.4%), and cryptogenic cirrhosis in 6 (23.1%).

Presentations and Outcomes

Patients without cirrhosis

Both non-cirrhotic patients, one with NAFLD and other with EHPVO, presented with respiratory symptoms. None of the two developed liver-related complications. The LFTs were normal at admission in both patients. The patient with EHPVO was pregnant at the time of admission and had gestational diabetes mellitus (GDM). Both these patients recovered uneventfully without the need for oxygen or mechanical ventilation.

Patients with compensated cirrhosis

One patient had NAFLD-related compensated cirrhosis with baseline Child-Pugh-Turcotte (CTP) score of 5, and a MELD score of 9. His associated comorbidities included diabetes mellitus (DM) and coronary artery disease (CAD). He presented with respiratory symptoms and developed ACLF (grade III) during his hospital stay with respiratory, cardiovascular and renal failures. The patient succumbed to multiorgan failure on day 4 of hospital admission. The clinical severity of COVID–19 was severe in this patient.

Patients with AD

Sixteen patients had AD. The mean age was 48.6 ± 10.6 years, and 12 (75%) were males. The clinical presentations included primarily features of AD in 10 (62.5%), AD as well as respiratory complications in 5 (31.3%) and respiratory alone in one (6.3%). Among the 10 patients presenting with AD- 8 had upper gastrointestinal bleeding (UGIB), and 2 had ascites. In the combined presentation, AD included- 3 with UGIB and 2 with ascites, and respiratory- 4 had pneumonia and one had upper respiratory tract infection. One patient presented with pneumonia alone and during the hospital stay developed UGIB. Nine (56.3%) of these patients had a history of DM. The etiologies of cirrhosis included alcohol in 6 (37.5%), HBV, HCV and NAFLD in 1 (6.3%) each, AIH in 2 (12.5%), and cryptogenic in 5 (31.3%). The LFTs were as follows- bilirubin 1.4 ± 0.8 mg/dL, AST 50 (37–82) IU/L, ALT 29 (19–42) IU/L, ALP 102 (75–299) IU/L, albumin 3.0 ± 0.8 g/dL and international normalised ratio (INR) of 1.3 ± 0.2. The mean CTP and MELD score was 7.2 ± 1.6 and 12.1 ± 3.1, respectively. At presentation deranged LFT values included bilirubin (>1 mg/dL) in 10 (62.5%), AST (>40 IU/L) in 10 (62.5%), ALT (>40 IU/L) in 4 (25%) and alkaline phosphatase (>280 IU/L) in 4 (25%). Median hospital stay was 8 (6 - 17) days in 16 patients with AD. Of these, 15 (93.8%) recovered and were discharged. One patient (6.3%) required invasive mechanical ventilation and succumbed to illness after developing grade III ACLF (cardiovascular, respiratory, renal and cerebral failure). Overall, COVID–19 severity was mild in 14 (87.5%), moderate and severe in 1 (6.3%) each.

Patients with ACLF

Nine patients had ACLF at presentation; the mean age was 47.4 ± 13.6 years, and 6 (67%) were males. Of these 9 patients- Grade I, II and III ACLF were present in 3 (33%), 2 (22.2%) and 4 (44.4%), respectively. The etiology of cirrhosis included alcohol in 3 (33%), HBV and AIH in 2 (22%) each, and HCV and cryptogenic in one (11%) each. The clinical presentations included- complications of cirrhosis along with respiratory complaints in 6 (67%), complications of cirrhosis alone in 2 (22%) and only respiratory complaints in one patient.

Three (33%) patients with ACLF had DM. The LFTs were as follows- bilirubin 5.3 (3.4–18.4) mg/dL, AST 75 (61–140) IU/L, ALT 37 (25–59) IU/L, ALP 174 (88–489) IU/L, albumin 2.8 ± 0.7 g/dL and INR 2.6 ± 1.2.

The mean CTP, MELD score and chronic liver failure-consortium organ failure (CLIF-C OF) and CLIF-C ACLF scores were 11.1 ± 0.9, 28.4 ± 7.7, 13.8 ± 2.7 and 58.0 ±13.6, respectively. At presentation, deranged bilirubin and AST were seen in all, ALT in 4 (44%) and Alkaline phosphatase in 4 (44%). Of the 9 patients with ACLF, all died over a median hospital stay of 7 (5 - 8) days. The cause of death was acute respiratory distress syndrome with multiorgan failure in all 9 (100%) patients. Overall, COVID–19 severity was severe in 7 (77.8%), mild and moderate in 1 (11.1%) patient each.

Comparison of characteristics between cirrhotic patients with COVID–19 and historical controls

We compared COVID–19 patients with cirrhosis (n = 26) with age, sex and severity matched historical controls (n = 78), from a previously published data from our center (Table 1). There was no difference in characteristics between the COVID-positive cases and historical controls except platelet count and alkaline phosphatase, which were higher in historical controls.

Overall, the mortality rate was higher in cirrhosis patients with COVID–19 [11/26 (42.3%) vs 18/78 (23.1%)]; though, the difference just fell short of statistical significance (p = 0.077). The mortality rate among COVID–19 patients presenting as ACLF was 100% (9/9), while that in historical controls with ACLF was 53.3% (16/30), p = 0.015. The mortality rate among COVID–19 patients presenting as compensated cirrhosis and AD was 11.8% (2/17), compared to 4.2% (2/48) among historical controls (p = 0.278). There were no differences between the prognostic scores of ACLF patients with COVID–19 and historical controls- MELD (28.4 ± 7.7 vs 30.9 ± 6.6, p = 0.347), and CLIF-C ACLF score (58.0 ± 13.6 vs 50.8 ± 10.7, p = 0.107).

Predictors of mortality

On univariate analysis, the factors significant for outcome among COVID–19 patients were total leucocyte count (TLC), total bilirubin, creatinine, INR, CTP score, MELD score and requirement of invasive ventilation (Table 2). On multivariate analysis only mechanical ventilation was independently associated with mortality HR, 13.680 (1.390- 134.582, P = 0.025) after adjusting for MELD, and TLC

Use of COVID specific drugs

Twenty-five patients received specific drugs for COVID–19 infection: HCQ- 21 (84%), low molecular weight heparin (LMWH) 5 (20%), Vitamin C 22 (88%), zinc 10 (40%), Azithromycin 20 (80%), ivermectin 13 (52%), and methylprednisolone 5 (20%).

Discussion

In this analysis from a tertiary care center in India we describe the clinical presentations and outcomes of COVID–19 infection in patients with underlying liver disease. Over 8 weeks, we noted 28 patients with underlying liver disease presenting with COVID–19 infection. A higher number of patients reported in the latter part of the study were in accordance with the increasing incidence of COVID–19 infections in India [15]. Overall, COVID–19 severity was mild in 15 (57.7%), moderate in 2 (7.7%) and severe in 9 (34.6%), We observed that COVID–19 patients with cirrhosis presented with complications of cirrhosis in 12 (46.2%), respiratory symptoms in 3 (11.5%) and combined complications of cirrhosis and respiratory symptoms in 11 (42.3%). The high rate of respiratory symptoms is expected as SARS-CoV–2 is transmitted via the respiratory route. Our data suggest that cirrhosis patients presenting with respiratory symptoms and recent onset of decompensation/deterioration of underlying liver disease should be evaluated for SARS-CoV–2 infection. Patients with cirrhosis and ACLF are at increased risk of severe COVID–19 infection

because of impaired immune status. We observed patients with compensated cirrhosis deteriorate after COVID–19 infection. Furthermore, none of ACLF patients with concomitant COVID–19 survived in our study, as compared to 47% survival rate in ACLF patients of historical control. The presence of pneumonia in more than 50% of patients in the COVID–19 group could have led to a higher proportion of patients developing AD and ACLF. On multivariate analysis, we found requirement of invasive ventilation to be an independent predictor of outcome in COVID positive patients. The higher mortality rates in COVID–19 patients could possibly could be because of extrahepatic organ failures especially respiratory failure. The severity of lung injury and CLIF-C have been associated with poor outcomes in COVID–19 patients with cirrhosis [16]. Pulmonary vascular changes including capillary microthrombi, are common in patients with COVID–19 [17]. The exact mechanisms related to poor outcomes needs exploration.

The outcome parameters in our study are similar to those reported by a multicenter registry (dated 19th June 2020)- (Surveillance Epidemiology of Coronavirus) Under Research Exclusion (SECURE)-CIRRHOSIS registry and EASL supported COVID-Hep [7]. The registry reported the outcome of 833 patients with CLD. Of the 303 patients with CLD without cirrhosis, the requirement of invasive ventilation was 18%, and mortality was 8%. Among the 379 patients with cirrhosis (alcohol 32%, non-alcoholic steatohepatitis 20%, viral 18% and alcohol and HCV combined 5%) decompensation occurred in 45%, the requirement of invasive ventilation was 19% and death occurred in 33%. Among the 151-liver transplant (LT) patients, the requirement of invasive ventilation was 19%, and death occurred in 19% of patients. These results suggest that patients with cirrhosis are at a higher risk of mortality post-COVID–19 infection.

Infections are common in patients with ACLF and are associated with poor outcomes [9]. Whether SARS-CoV–2 infection outcomes are similar to other acute precipitants, including bacterial infection in patients developing ACLF, is unclear. A recent study reported poor outcomes in COVID–19 positive patients as compared to those with bacterial infection [16]. The definite management of ACLF is LT. The current society guidelines differ in their opinion regarding LT in the current scenario. The American Association for the Study of Liver disease (AASLD) recommends not to postpone transplants as it is an essential medical service while the EASL and Asian Pacific Association for the Study of the Liver (APASL) recommend restricting transplants to those with poor short term prognosis [18]. The medical treatment options that have been tried for management of COVID–19 patients include drugs like hydroxychloroquine, remdesivir, other antivirals, and plasma therapy. None of these therapies have been shown to definitely improve the outcome. Moreover, most of these have hepatic side effects. Therefore, there is an urgent need for effective therapies to improve outcomes. We followed the standard recommendation for the management of all complications. For patients who presented with UGIB, we delayed endoscopy and managed patients with vasoconstrictors like terlipressin and patients were started on carvedilol for secondary prophylaxis [19]. All the patients could be managed medically without an increased risk of rebleeding.

We found that the proportion of patients with COVID–19 with alcohol etiology was less as compared to our previous experience [20]. In the pre-COVID era, the highest fraction of CLD patients admitted was due to alcohol etiology [9]. Lockdown was implemented by the Indian government, and alcohol was not

available; this could be a reason, and another possible reason could be the fact the borders of the states were sealed, which would reduce the number of patients reaching the hospital.

The derangement of liver function tests at presentations has been reported in up to 50% of patients without liver disease [21]. The exact significance of the rise in transaminases and its relation to outcomes is unclear. The rise in liver enzymes could be multifactorial due to drugs side effects, associated ischemic hepatitis, and possibly related to SARS-CoV–2 infection per se or the associated cytokine storm [2].

Limitations of the study include its descriptive nature. Due to a small number of patients, we cannot rule out chances of type II statistical errors. The comparison group was taken from historical control admitted during different time frame. The drug therapies varied as per the evolving guidelines and treating team's consensus. Our center is a tertiary care center; the proportion of patients with advanced liver disease was higher as compared to chronic hepatitis and compensated cirrhosis. Our results need to be validated in larger sample size before generalization.

In conclusion, COVID–19 infection in patients presenting as ACLF is associated with a poor outcome. Overall, in cirrhotic patients, COVID–19 appears to confer higher mortality as compared to those without it. Mechanical ventilation is associated with a poor outcome. In the absence of definite therapies available for COVID–19, it is imperative to prevent infection in patients with cirrhosis.

Declarations

Conflict of Interest statement: S, AE , MV, RK, PP, KDS, RA, MS, PJ, AK, PK, AKS, AB, NN, LD, AC, KR, AM, PA, BN, DG, AS, SM, GM, AT and PG declare that they do not have any conflict of interest to report.

Ethics statement: The study was carried out after approval from the Institutional Ethics Committee, All India Institute of Medical Sciences, New Delhi (Ref No: IEC- 253/17.04.2020). The study was performed in accordance with the declaration of Helsinki, revised in 2000

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Tables

Table 1. Comparison of COVID-positive and historical controls with cirrhosis.

Characteristics	COVID-positive (n=26)	Historical Controls- Cirrhosis patients	P-value
		(n=78)	
Mean Age (years)	48.5 ± 12.1	49.1 ± 11.7	0.804
Sex, male n (%)	19 (73.1%)	56 (70.0%)	1.000
Etiology of cirrhosis Alcohol			0.923
	9 (34.6%)	27 (34.6%)	
Viral	5 (19.2%)	14 (17.9%)	
AIH	4 (15.4%)	8 (10.3%)	
Cryptogenic	6 (23.1%)	24 (30.8%)	
Others	2 (7.7%)	5 (6.4%)	
Clinical presentation Compensated cirrhosis and AD	17 (65.4%)	48 (61.5%)	0.817
ACLF	9 (34.6%)	30 (38.5%)	
ACLF grade (I/II/III)	3/2/4	10/6/14	0.988
Hemoglobin (g/dL)	8.8 ± 3.2	8.7 ± 2.9	0.864
Total leucocyte count (per mm3)	7070 (5075-12900)	8500 (4775-10875)	0.719
Platelet count (x103/mm3)	71.5 (47.5-119.2)	101.5 (61.5-161.2)	0.020
INR	1.7 ± 1.0	1.9 ± 0.9	0.355
Total Bilirubin (mg/dL)	2.1 (1.0-4.2)	2.0 (0.9-6.9)	0.747
Creatinine	1.5 ± 1.3	1.2 ± 1.0	0.266
AST (IU/L)	67 (43-108)	63 (40-126)	0.867
ALT (IU/L)	30 (22-50)	42 (24-78)	0.067
Alk P (IU/L)	111 (85-303)	268 (195-406)	<0.001
Albumin (g/dL)	2.8 ± 0.7	3.2 ± 0.9	0.123
CTP	8.6 ± 2.3	9.5 ± 2.8	0.149
MELD	18.1 ± 9.6	19.6 ± 10.2	0.528
Death (%)	11 (42.3%)	18 (23.1%)	0.077

Abbreviations: AD, acute decompensation; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; Alk P, alkaline phosphatase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease.

Table 2. Univariate analysis of predictors of in-hospital mortality in COVID-19 positive cirrhosis patients.

Variable	Univariate HR	P-value
Mean Age (years)	1.024 (0.969-1.083)	0.397
Sex, female n (%)	1.277 (0.329-4.959)	0.723
Diabetes, present	0.648 (0.183-2.297)	0.501
Hemoglobin (g/dL)	1.043 (0.874-1.245)	0.637
Total leucocyte count (per mm3)	1.061 (0.989-1.138)	0.096
Platelet count (x103/mm3)	1.002 (0.996-1.009)	0.468
INR	1.482 (1.000-2.195)	0.050
Total Bilirubin (mg/dL)	1.060 (1.009-1.114)	0.021
Creatinine	1.504 (1.010-2.238)	0.044
AST (IU/L)	1.005 (0.999-1.012)	0.109
ALT (IU/L)	1.013 (.984-1.043)	0.372
Alk P (IU/L)	1.002 (0.999-1.005)	0.188
Albumin (g/dL)	0.943 (0.404-2.200)	0.891
CTP	1.680 (1.205-2.341)	0.002
MELD	1.084 (1.026-1.146)	0.004
Requirement of invasive ventilation	18.858 (2.406-147.809)	0.005

Abbreviations: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh; INR, international normalized ratio; MELD, model for end-stage liver disease.