Outcomes of COVID-19 in Patients with Cirrhosis or Liver Transplantation

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Coronavirus disease 2019 (COVID-19) is associated with a significant morbidity and mortality in patients with cirrhosis. There is a significantly higher morbidity and mortality due to COVID-19 in patients with decompensated cirrhosis as compared to compensated cirrhosis, and in patients with cirrhosis as compared to noncirrhotic chronic liver disease. The fear of COVID-19 before or after liver transplantation has lead to a significant reduction in liver transplantation numbers, and patients with decompensated cirrhosis remain at risk of wait list mortality. The studies in liver transplantation recipients show that risk of mortality due to COVID-19 is generally driven by higher age and comorbidities. The current review discusses available literature regarding outcomes of COVID-19 in patients with cirrhosis and outcomes in liver transplant recipients. (J Clin Exp Hepatol 2021;11:713–719)

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related coronavirus disease 2019 (COVID-19) is a recent pandemic that has overwhelmed the healthcare system in many countries due to large number of patients getting admitted and requiring intensive care. There is no approved treatment for this disease at present. The COVID-19 is associated with significant morbidity and mortality in patients with liver disease when compared to general population.[1–3] Several studies have shown a significant risk of mortality in patients with cirrhosis and in liver transplantation recipients.[2–4] The severity of presentation and risk of mortality is more in patients with decompensated cirrhosis.[5,6] COVID-19 had lead to a significant decrease in number of liver transplant surgeries being performed, which would lead to an increased wait list mortality in these patients.[7] The present review discusses possible pathogenesis of COVID-19 associated liver injury, and mortality due to COVID-19 in patients with no liver disease, in patients with noncirrhotic chronic liver disease, in patients with cirrhosis and in liver transplantation (LT) recipients.

PATHOGENESIS OF LIVER INJURY BY SARS-COV-2 AND INCIDENCE OF RAISED LIVER FUNCTION TESTS IN PATIENTS WITH COVID-19

SARS-CoV-2 enters liver cells through angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptors. ACE2 is mainly expressed on cholangiocytes and less on hepatocytes. Both these cells help in regeneration of the liver after liver injury. The infection of the cholangiocytes and progenitor cell population may lead to decreased regenerative capabilities of the liver. The liver injury in COVID-19 might be partly due to direct injury of cholangiocytes, and deterioration of liver function may happen due to impaired regeneration.[8,9] Patients with cirrhosis are more predisposed to acute liver injury due to upregulated expression of ACE2 protein (thus facilitating more viral entry into cells). Patients with decompensated cirrhosis have more expression of ACE2 protein as compared to patients with compensated cirrhosis, thus making them more susceptible to acute liver injury by virus, in presence of already impaired regeneration capacity due to baseline-decompensated cirrhosis.[10,11]

Abnormal liver function tests (LFT) are common in patients with COVID-19 in absence of chronic liver disease. A systematic review by Ghoshal et al showed that 10.5%–53% of patients with COVID-19 had raised liver enzymes, although jaundice was uncommon as the total bilirubin was raised in only 5–18% patients. A reduction in serum albumin is also reported by several studies. Patients with more severe COVID-19 associated disease had liver function test abnormalities more often.[12] Izcovich et al

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Abbreviations: ACE: angiotensin-converting enzyme related carboxypeptidase receptors; ACLF: acute-on chronic liver failure; ALI: acute liver injury; ALT: alanine transaminase; AST: aspartate aminotransferase; CLD: chronic liver disease; COVID-19: Coronavirus disease 2019; HCWs: health care workers; HR: hazard ratio; LFT: liver function tests; LT: liver transplantation; MELD: model for end-stage liver disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; OR: Odds ratio; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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conducted a systematic review of 207 studies and found several variables that provided prognostic information about severe disease and/or mortality. High blood aspartate aminotransferase (AST), decrease in albumin and high blood bilirubin are associated with severe disease.[13] Patients with abnormal LFTs have a worse prognosis as compared to those with normal LFT. Wu et al also looked at prognosis of abnormal LFTs in a meta-analysis by 45 studies,[14] the pooled incidence of any abnormal liver biochemistry at admission was 27.2% and during hospitalization 36%. At admission, abnormal albumin was the most common finding (39.8%) followed by gamma-glutamyl transferase (35.8%), AST (21.8%), alanine transaminase (ALT) (20.4%), total bilirubin (8.8%) and alkaline phosphatase (4.7%). During hospitalization, abnormal ALT, AST and total bilirubin were present in 38.4%, 28.1% and 23.2%, respectively. Severe and or critical patients and nonsurvivors had a higher incidence of abnormal liver biochemical indicators. It should be noted that abnormal LFTs might be related to drugs or secondary to ischemia (if present) in addition to direct effects of COVID-19.[14]

Although patients with noncirrhotic chronic liver disease (CLD) may not have a higher mortality, patients with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) may have more disease severity/mortality due to frequent association with diabetes, obesity, and metabolic syndrome.[15,16]

It is important to understand that these studies mainly detect case fatality rate (diagnosed cases) and not infection fatality rate (as asymptomatic or mild cases may not get tested). A systematic review of 73 studies (n = 24,299) showed that 3% patients with COVID-19 were suffering from underlying CLD. The presence of CLD was significantly associated with more severe infection (pooled odds ratio [OR] 1.48) and overall mortality (pooled OR 1.78). Moreover, there was a nonsignificant trend for increased ICU and invasive mechanical ventilation requirement in patients with CLD.[2] In a multicentric United States study, the presence of CLD and NAFLD was independently associated with ICU stay and mechanical ventilation. The presence of cirrhosis was a significant predictor of mortality (adjusted OR 12.5, 95% confidence interval [CI] 2.16–72.5).[17]

Patients with liver disease, in particular patients with NASH, may have higher comorbidities then non-liver disease patients. Singh et al compared 250 patients with liver disease (NASH being the most common sitology) to 2530 non-liver disease patients in a multicentric study. The patients in the liver disease group were older and had higher comorbidities, including hypertension in 68% and diabetes in 48%. The authors found that the patients with liver disease were at significantly increased risk for mortality (RR, 2.8; 95% CI, 1.9–4.0; $P < 0.001$) after 1:1 propensity score matching.[18] Ioannou et al identified 88,747 patients tested for COVID-19 in the Veterans Affairs national healthcare system. The following groups were studied: no cirrhosis-SARS-CoV-2 negative (C0–S0, n = 75,315), no cirrhosis-SARS-CoV-2 positive (C0–S1, n = 9826); cirrhosis-SARS-CoV-2 negative (C1–S0, n = 3301); cirrhosis-SARS-CoV-2 positive (C1–S1, n = 305). The 30-day mortality and ventilation rates were 5.2% and 3.6% in C1–S0, and 17.1% and 13.0% in C1–S1. The patients with cirrhosis and a positive test for SARS-CoV-2 were more likely to undergo mechanical ventilation and mortality, risk being 4.1 times and 3.5 times, respectively. Higher age, decompensation, and high model for end-stage liver disease (MELD) score were predictors of mortality in patients with cirrhosis and SARS-CoV-2. Cirrhosis was associated with a 1.7 times increase in mortality in patients with SARS-CoV-2 infection.[19]

MORTALITY: NONCIRRHOTIC CHRONIC LIVER DISEASE VERSUS LIVER CIRRHOSIS

The risk of mortality increases with increasing severity of liver disease as shown in Figure 1. Studies showing outcomes of COVID-19 in patients with cirrhosis are shown in Table 1 (references[3,5,6,19–22]).

Sarin et al studied acute liver injury (ALI) and its impact on outcomes in patients with noncirrhotic chronic liver disease and with cirrhosis. The authors defined ALI as any one of the following: total bilirubin level of ≥3 mg/dl, acute increase in ALT, AST, SAP, gamma-glutamyl transpeptidase ≥2 times upper normal limit and prothrombin time-international normalized ratio of ≥1.5 with previously normal liver parameters. The study included 228 patients; 185 had a diagnosis of CLD without cirrhosis and 43 were suffering from cirrhosis. In patients with CLD without cirrhosis; diabetes (OR = 2.1, $P = 0.01$) and in patients with cirrhosis; obesity (OR = 8.1, $P = 0.002$) predisposed more to liver injury than those without these risk factors. Forty-three percent of CLD noncirrhotic presented as ALI, while 20% of cirrhotics presented with either acute-on-chronic liver failure [11.6%) or acute decompensation (9%). A Child-Turcotte-Pugh score of 9 or more at presentation predicted mortality (area under curve 0.94, sensitivity 85.7% and specificity 94.4%, hazard ratio [HR] 19.2 [95 CI 2.3–163.3], $P < 0.001$). The liver injury was progressive in 57% of patients with decompensated cirrhosis and 43% died. A rising bilirubin and AST/ALT ratio predicted mortality in patients with cirrhosis.[5] Marjot et al compared 386 patients with and 359 without cirrhosis and COVID-19 (data from two international registries). The authors compared this data with non-CLD patients with COVID-19 from a UK hospital network. Mortality was 8% in those without cirrhosis, compared to 32% in patients with cirrhosis. Mortality increased with Child-Turcotte-Pugh severity; 19%, 35% and 51% in patient s with class A, B and C, respectively. Higher age, presence of cirrhosis (more risk in CTP B or C),

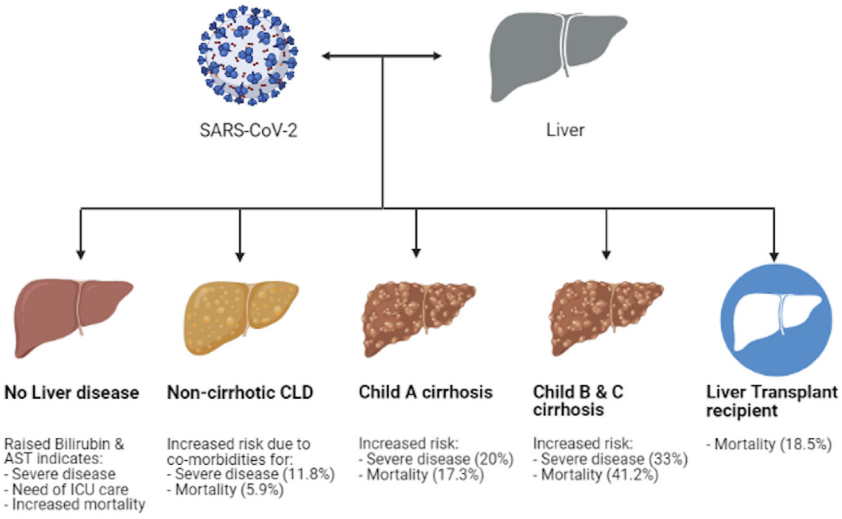

Figure 1 Mortality in COVID-19, data based on references[5,22] and Table 2.

and alcohol-related liver disease were risk factors for mortality.[22]

Mortality in patients with COVID-19 and cirrhosis is driven mainly by severity of liver disease. An international registry showed that 47 patients of 152 patients died. The nonsurvivor group had significantly high prevalence of cirrhosis (versus no cirrhosis) and decompensated cirrhosis (Child class B or C 25.7% in survivors versus

Table 1 Outcomes of COVID-19 in Patients with Cirrhosis.

Author (ref.)	n	Mortality/results	Comments
Shalimar[20]	26 cirrhotics	11/26 (42.3%) died	Requirement of mechanical ventilation independently predicted mortality (hazard ratio 13.68)
Sarin[5]	43 cirrhotics versus 185 CLD-no cirrhosis	7/43 (16.3%) cirrhosis vs 5/185 (2.7%) CLD- no cirrhosis	Nearly twice mortality in decompensated cirrhosis (versus compensated), Child-Turcotte Pugh score of 9 or more at presentation predicted high mortality AUROC 0.94, HR = 19.2 (95 CI 2.3–163.3), $P < 0.001$)
Iavarone[3]	50 cirrhotics	30-day mortality rate of 34% (n = 17)	Higher mortality in patients with respiratory failure and in those with worsening liver function
Ioannou[19]	305 cirrhotics	55 (18%)	Higher age, decompensation, and high MELD score were predictors of mortality
Moon[6]	103 cirrhotics, 49 non-cirrhotic CLD	Mortality occurred in 12.2% of patients with CLD without cirrhosis, 23.9% with Child-Pugh class A cirrhosis, 43.3% with Child-Pugh class B cirrhosis, and 63.0% with Child-Pugh class C cirrhosis	Child-Pugh class B and C cirrhosis remained associated with death after adjusting for baseline characteristics
Kim[21]	867 patients (including 134 compensated and 93 decompensated cirrhotics)	19/134 (14.1%) of compensated, 38/93 (40.8%) of decompensated, 9/22 (40.9%) of patients with hepatocellular carcinoma	Alcohol related liver disease, decompensated cirrhosis, and HCC predicted higher overall mortality
Marjot[22]	386 cirrhosis, 359 without cirrhosis	Mortality was 8% in without cirrhosis, 32% in patients with cirrhosis	Mortality 19%, 35% and 51% and Child-Pugh class A, B and C respectively

63.9% in non-survivors). A total of 43% (13/30) of patients in Child class B and 62.9% (17/27) patients in Child class C died. The mortality rate was 12.2% (6 out of 49) for noncirrhotic CLD, 23.9% (11 out of 46) for Child class A cirrhosis and 52.5% for decompensated cirrhosis (30 out of 57). MELD was also significantly high in nonsurvivors. On multivariate analysis, higher age, body mass index >30 kg/m^2, and Child class B and C were significantly associated with mortality.[6] In another multicenter retrospective study, patients with cirrhosis and severe acute COVID-19, Iavarone et al demonstrated that a 30-day mortality rate of 34% (17 out of 50) in patients with cirrhosis, which was significantly higher than a comparative cohort of cirrhosis and bacterial infections (17%) and patients without cirrhosis (18%). The severity of lung and liver diseases predicted mortality.[3] Other predictors of mortality due to COVID-19 in patients suffering from cirrhosis include need of mechanical ventilation (thus severe pulmonary disease) and Charlson comorbidity -index.[20,23]

MORTALITY IN PATIENTS WITH COVID-19 RELATED ACUTE-ON-CHRONIC LIVER FAILURE

COVID-19 can cause decompensation or worsening of baseline cirrhosis. Iavarone et al showed that severe COVID-19 in patients with cirrhosis leads to significant increase of bilirubin, prothrombin time, and creatinine, also albumin decrease significantly. Patients with a MELD score ≥15 increased from 13% to 26% (P = 0.037), acute-on-chronic liver failure (ACLF) and acute liver injury occurred in 14 (28%) and 10 (20%) patients.[3] In the study by Moon et al, 25% (39 out of 152) had new decompensation event after diagnosis of COVID-19 and 24 of these patients died.[6] ACLF related to COVID-19 is common and is associated with significant risk of mortality. In the study by Shalimar et al, 9 patients had ACLF, all of whom died. The mortality in COVID-19 related ACLF was significantly higher than historical controls with ACLF.[20] In an Indian study of 57 patients with cirrhosis and COVID-19, 20 (35%) presented as ACLF. The patients in the ACLF group had significantly prolonged hospital stay severe COVID-19 illness, need for intensive care unit, and higher mortality (30% versus 5%). Patients who died in the ACLF group had significantly higher Chronic Liver Failure Consortium (CLIF C) score, CLIF C organ failure score, and ACLF grade.[24] The study by Marjot et al found that 50% (89 out of 189) of patients with cirrhosis and acute hepatic decompensation developed ACLF. Among patients with cirrhosis, the mortality was higher in patients with ACLF than in those without ACLF (65% versus 22%).[22]

LIVER TRANSPLANTATION DURING THE COVID-19 PANDEMIC

Liver transplantation (LT) remains the only definitive treatment for patients with decompensated cirrhosis. COVID-19 has affected LT in multiple ways; patients with cirrhosis are at risk of wait list mortality due to COVID-19 infection or due to delay in a timely transplant. In addition, there is

Table 2 Outcomes of LT Recipients with COVID-19 Infection.

Author reference	n	Outcomes, comments
Belli[33]	243	European Liver and Intestine Transplantation Association registry, 49 (20.2%) died, higher age (>70 years) predicted mortality, use of tacrolimus was protective. After excluding age, diabetes and chronic kidney disease significantly associated with mortality
Polak[4]	244	36 (14.7%) died, Internet-based survey
Webb[34]	39	Data from registry, 9 (23%) died, 4 of death happened in patients transplanted < 2 years back, 4 of died had diabetes and hypertension, 3 were obese
Rabiee[35]	112	25 (22.3%) died, LT recipients had lower acute liver injury when compared to age- and sex-matched CLD, reduction of immunosuppression was not associated with liver injury/mortality. ALI significantly associated with mortality
Lee[36]	38	7 died (18% overall, 29% of hospitalized)
Dumortier[37]	104	20 died, age independently associated with mortality
Becchetti[38]	57	7 died (12%), 5 of 7 mortalities happened in cases with history of cancers
Colmenero[39]	111	31.5% had severe disease, 20 (18%) mortality
Webb[40]	151	28 (19%) died, when compared to matched nontransplant population, mortality was not high in transplant recipients
Dhampalwar[41]	12	1 died
Case reports or small series[32,42–46]	27	9 died
Total	1138	211 died (18.5%)

risk of COVID-19 infection after transplant. A patient remains at risk of getting infection at hospital as virus remains infectious from several hours to few days on various surfaces,[25] or from an infected health care worker (HCW). If the patient with cirrhosis or liver transplant is suffering from COVID-19 also, it carries risk of infecting HCWs. The situation of HCWs getting infected becomes more complex if some patients with COVID-19 remain asymptomatic, and there is a risk of spreading infection in the incubation period (World Health Organization report)[26] and the sensitivity of COVID polymerase chain reaction (PCR) is approximately 70%, which may lead to the under diagnosis of COVID-19 and potential exposure of HCWs to an infected but negative PCR patient.[27]

Various societies have suggested guidelines for this situation, which suggest deferring hospital visits and LT in stable patients.[28–30] Number of LT performed has decreased in the COVID-19 era, both deceased donor and living donor LTs.[7,31,32] As a result, LT is being done for more sick patients as compared to earlier. We compared LT in the COVID-19 era and in the same period of 2019. While a total of 39 LTs were performed from March 15th to June 10th in 2019, the number of LTs decreased to 23 (59% of 2019) in 2020. The adult patients with cirrhosis had significantly higher MELD score in year 2020 (19.8 ± 7.0 versus 16.1 ± 5.6 in 2019), $P = 0.034$.[7]

MORTALITY IN LIVER TRANSPLANT RECIPIENTS VERSUS NONTRANSPLANT PATIENTS

Table 2 discusses outcomes of COVID-19 in liver transplantation recipients (references[4,33–46]). Belli et al reported data from 36 centers across Europe. The study included 243 adult LT recipients suffering from symptomatic COVID-19. Thirty-nine recipients (16%) were managed as outpatients, 84% were hospitalized. Forty-nine patients (20.2%) died due to respiratory failure as the major cause. Following factors predicted mortality on multivariable analysis: age >70 (HR, 4.16; 95% CI, 1.78–9.73) and tacrolimus use (protective effect, HR, 0.55; 95% CI, 0.31–0.99). In a model excluding age, both diabetes and chronic kidney disease were significantly associated with mortality.[37]

A prospective Spanish study of 111 LT recipients with COVID-19 infection showed 18% mortality in LT recipients, this mortality rate was lower than matched general population. Thirty-five patients (31.5%) had severe COVID-19. The use of mycophenolate at baseline was an independent predictor of severe COVID-19 disease, this effect was not observed with calcineurin inhibitors or everolimus.[39] Another study by Webb et al also did not find a higher mortality in LT recipients with COVID-19; mortality in LT recipients was similar to matched population without liver transplantation.[40] The authors compared adult LT recipients with severe COVID-19 (n = 151) from a multicenter database (18 countries) to matched patients (n = 627). The mortality was 19% in transplant cohort versus 27% in control cohort, $P = 0.046$. The authors found that increased age and comorbidities were related to mortality.[40]

Rabiee et al compared 112 adult LT recipients with COVID-19 to age- and sex-matched 375 CLD with COVID-19. The mortality rate was 22.3% in LT recipients, 72.3% were hospitalized and 26.8% were admitted to the intensive care unit. A reduction in immunosuppression was not associated with ALI or mortality. The ALI was significantly associated with mortality ($P = 0.007$; OR, 6.91) and ICU admission ($P = 0.007$; OR, 7.93) in LT recipients.[35] In French solid organ transplant registry, 104 patients were diagnosed with COVID-19 at a median of 92.8 months (interquartile range 40–194 months) after LT. One-third suffered from severe COVID-19, and the 30-day mortality was 20% (28.1% for hospitalized patients). Multivariate analysis showed age to be independently associated with mortality.[37]

MORTALITY IN EARLY VERSUS LATE COVID-19 INFECTION AFTER LT

An important issue with LT during the pandemic is recipient outcome in case of COVID-19 infection in the early post-surgery period. There is scarce data on outcomes of early COVID-19 after LT. As discussed previously, studies have shown that LT recipients with higher age and comorbidities have higher mortality; relation of mortality to time since transplantation is not established. Mortality in LT recipients due to COVID-19 infection is a complex interplay of comorbidities and immunosuppression. Bhoori et al described 3 mortalities in LT recipients due to COVID-19. All these mortalities happened in recipients with a post-transplant follow-uP > 10 years. All 3 males were older than 65 years, had obesity, diabetes, hyperlipidemia, and hypertension. Three patients had COVID-19 at <2 years after LT, all did well.[43] We published data of 12 LT recipients with COVID-19.[41] One of these patient (8.3%) died; the patient who died was a 60-year-old male with comorbidities of diabetes, hypertension, metabolic syndrome, and chronic rejection. He underwent LT 82 months back.[41] Although patients with longer follow-up after LT (thus on less immunosuppression) been shown to have higher mortality in some studies, the finding is biased by higher age and higher chances of having comorbidities in LT recipients with long-term follow-up. Several small series have shown mortality in early period after LT. Maggi et al also showed that one of two LT recipients died postoperatively due to COVID-19.[32] Recently two centers have reported outcomes of early COVID-19 after LT. Massoumi et al described 5 patients with early COVID-19; 3 were mild cases while 2 were moderate cases.[45]

Waisberg et al described their experience of 7 patients with early COVID-19 (range 9–39 days) after LT. Three of these patients had severe disease and 2 died. This series

had several important differences from series by Massoumi et al. The patients were older and had more comorbidities, and most of the patients were diagnosed with COVID-19 at the index hospitalization.[46]

A systematic review of 12 studies (n = 517 hospitalized LT recipients with COVID-19) found the following presenting symptoms: fever (71%), cough (62%), dyspnea (48%), and diarrhea (28%). There was a higher mortality risk in age group >60–65 years (OR 4.26; 95% CI, 2.14–8.49). Duration since transplant did not affect outcome.[47]

While immunosuppression may attenuate inflammatory response to COVID-19, it may also increase virological injury and risk of secondary infections and may prolong viral shedding. Mortality in LT recipients appears to be driven by higher age and comorbidities rather than by higher or lower immunosuppression.

The COVID-19 is associated with a significant risk of more severe disease presentation and mortality in patients with cirrhosis. The risk of mortality is more in patients with decompensated cirrhosis. There is limited data of COVID-19 in liver transplant recipients, which suggests that mortality after LT depends on higher age and comorbidities. Given the current situation of a significant number of patients with COVID-19 in the community, we propose to defer elective liver transplantation for relatively stable patients who can wait for several months. As sick patients will have higher mortality during a long waiting period or in case of COVID-19 infection, emergency liver transplantation should not be deferred.

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NSC, NS: conceptualization; NSC, SW: draft writing; NS, ASS: critical revision.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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