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Review Article

Coronavirus Disease-2019 (COVID-19) and the Liver

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Abstract

Within a year of its emergence, coronavirus disease-2019 (COVID-19) has evolved into a pandemic. What has emerged during the past 1 year is that, apart from its potentially fatal respiratory presentation from which the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) derives its name, it presents with a myriad of gastrointestinal (GI) and liver manifestations. Expression of the angiotensin-converting enzyme-2 (ACE-2) receptor throughout the GI tract and liver, which is the receptor for the SARS-CoV-2, may be responsible for the GI and liver manifestations. Besides acting directly via the ACE-2 receptor, the virus triggers a potent immune response, which might have a role in pathogenesis. The virus leads to derangement in liver function tests in close to 50% of the patients. The impact of these derangements in patients with a normal underlying liver seems to be innocuous. Severe clinical presentations include acute decompensation and acute-on-chronic liver failure in a patient with chronic liver disease, leading to high mortality. Evolving data suggests that, contrary to intuition, liver transplant recipients and patients with autoimmune liver disease on immunosuppression do not have increased mortality. The exact mechanism underlying why immunosuppressed patients fare well as compared to other patients remains to be deciphered. With newer variants of COVID-19, which can spread faster than the original strain, the data on hepatic manifestations needs to be updated to keep a step ahead of the virus.

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Abbreviations: ACE-2, angiotensin-converting enzyme-2; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; COVID-19, coronavirus disease-19; CSS, cytokine storm syndrome; DILI, drug-induced liver injury; GGT, gamma glutamyl transferase; GI, gastrointestinal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCQ, hydroxychloroquine; HCV, hepatitis C virus; ICU, intensive care unit; IHC, immunohistochemistry; IL, interleukin; INR, international normalized ratio; LFT, liver function test; LMWH, low molecular weight heparin; MELD, model for end-stage liver disease; mTOR, mammalian target of rapamycin; NACSELD, North American Consortium For The Study Of End-Stage Liver Disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RT-PCR, reverse transcription-polymerase chain reaction; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment; TMPRSS2, transmembrane serine protease 2; UGI, upper gastrointestinal; ULN, upper limit of normal.

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Introduction

The first case of coronavirus disease-2019 (COVID-19) was reported from Wuhan, China, in December 2019. Since then, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), responsible for COVID-19, has evolved into a pandemic, involving all continents to date (i.e. 31st January 2021).[1] SARS-CoV-2 is distinct from other coronavirus infections in that it manifests with a myriad of extra-pulmonary manifestations. Avid expression of the angiotensin-converting enzyme-2 (ACE-2) receptor throughout the gastrointestinal (GI) tract, including gastric, small intestinal and colonic mucosal cells, vascular endothelial cells, cholangiocytes and smooth muscle cells is the reason for the common occurrence of GI symptoms and hepatic manifestations.[2]

Pathogenesis of GI and liver manifestations

SARS-CoV-2 uses the spike protein (S) to bind to the ACE-2 receptor in target cells. The ACE-2 receptor is present on type 1 and 2 surface alveolar cells, leading to the predominant respiratory symptoms and the droplet mode of transmission. The ACE-2 receptor is also widely expressed throughout the GI tract (Fig. 1). On immunohistochemical (IHC) staining, Hamming *et al*.[2] demonstrated that the ACE-2 receptor is present in abundance in the vascular endothelium and smooth muscle cells of the vessels supplying the GI tract.

The pathophysiology of liver injury in COVID-19 is not as well established as its intestinal counterpart. In the liver, cholangiocytes and hepatic endothelial cells have been proposed to be the target cells for SARS-CoV-2.[3] Cholangiocytes express not only the ACE-2 receptor but also the transmembrane serine protease 2 (TMPRSS2), which cleaves the S protein of the virus prior to its entry into cells, thus providing the basis of cholangiocytes being highly vulnerable to SARS-CoV-2 damage.[4] It has also been shown in the liver ductal organoid model that SARS-CoV-2 leads to direct cytopathic changes in cholangiocytes, as hypothesized.[4] Histopathologic evaluation of autopsy and post-mortem biopsies reveal mild sinusoidal dilation with increased small lymphocyte infiltration. In addition, steatosis, multifocal hepatic necrosis without inflammatory cellular infiltration, and canalicular cholestasis have all been reported in the liver biopsies of patients with COVID-19 patients. Interestingly,

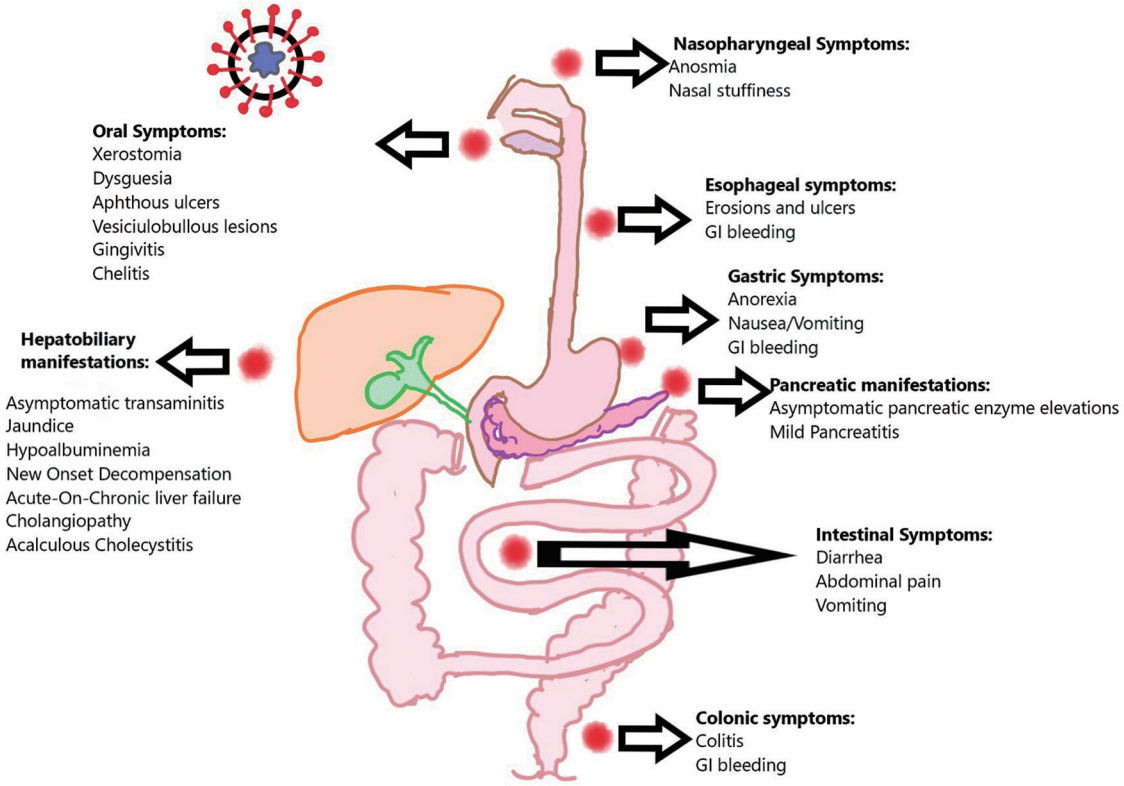

Fig. 1. GI and hepatic manifestations of COVID-19.

portal tract inflammation was not evident in these biopsies.[5] Sinusoidal dilation is attributed to cardiogenic venous outflow slowdown. It is well recognized that hypoxia and impaired cardiovascular function predispose the liver to injury. Both zones 1 and 3 show injury with no cellular infiltrate, ballooning, Mallory hyaline, or fibrosis. Several potential mechanisms have been postulated in the pathophysiology of liver manifestations, such as a direct viral insult, exacerbation of the underlying liver disease, hyperinflammatory states, and drug-induced injury, but evidence to support either mechanism is scanty.[6]

Liver manifestations of COVID-19

Hepatic injury is common in COVID-19 and is multifactorial. Possible reasons include direct hepatic involvement due to the virus, drug-induced liver injury (DILI) due to various therapeutic agents, hypotension, and the associated underlying liver disease (cirrhosis due to various etiologies, alcoholic steatohepatitis, non-alcoholic fatty liver disease, and viral hepatitis) (Fig. 2). The prevalence of GI and hepatic manifestations of COVID-19 is variable across studies from different regions, as highlighted in the data from meta-analyses (Table 1)[7–13] and individual studies (Table 2).[14–19] In addition, endemic areas are associated with co-infections, such as acute viral hepatitis, and tropical infections, such as malaria and dengue.[20–22]

Liver function test abnormalities

Alanine aminotransferase (ALT) elevations were seen in 4% to 33% of cases, according to China's initial reports,[23–25] and 39% of cases in a large study from New York, USA.[26] The prevalence of aspartate aminotransferase (AST) elevation ranged between 4% to 53% in a Chinese cohort and up to 58% in a USA cohort.[23,25,26] Both enzymes were mildly elevated in terms of absolute numbers and less than 5-times the upper limit of normal (ULN) in the majority. Kulkarni *et al*.[13] in their meta-analysis, placed the pooled incidence of AST and ALT elevation at 22.5% and 20.1%, respectively.

Elevation in gamma glutamyl transferase (GGT) has been reported in 13% to 54%, whereas elevation in alkaline phosphatase (ALP) is uncommonly elevated, in only 2% to 5% of cases.[27,28] In the meta-analysis by Kulkarni *et al*.,[13] the ALP and GGT elevation incidence was 6.1% and 21.1%, respectively. The rise in ALP may be disproportionate to other liver enzymes.

Hyperbilirubinemia may be seen in up to 18% of cases.[13,25,28] However, the derangement in the liver function tests can be multifactorial, as highlighted above, and it may be difficult to attribute to SARS-CoV-2-induced hepatic dysfunction alone.

Hypoalbuminemia has been described in severe COVID-19 patients and may not parallel changes in AST and ALT. In a retrospective cohort of 299 patients, 106 (35.5%) patients had low albumin, with significant differences in the albumin levels of survivors and non-survivors (37.6 g/L vs. 30.5 g/L).[29] Albumin levels have also been found to be an independent predictive factor for mortality.[29] In a meta-analysis of 1,990 patients across 14 studies, hypoalbuminemia was noted in 55.5%.[13] An important finding was that only 11% to 45.8% of patients with non-severe infection had hypoalbuminemia. In the severely ill, hypoalbuminemia was seen in up to 72.9%; whereas, among the deceased, hypoalbuminemia was reported in 78–100% cases, making

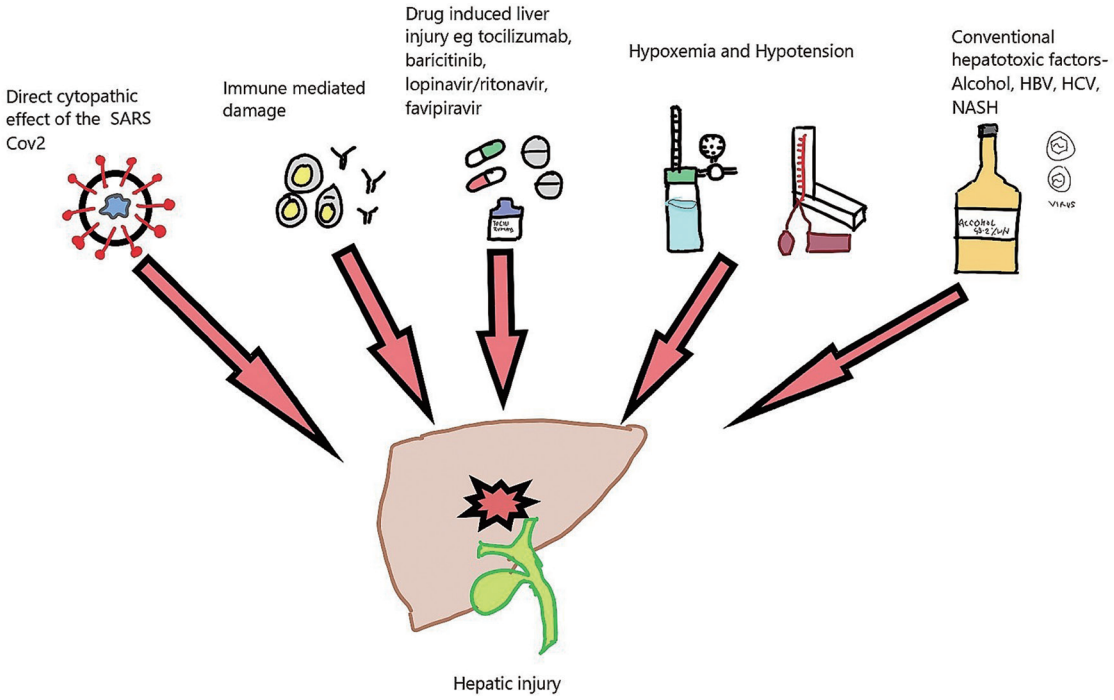

Fig. 2. Multifactorial nature of liver injury in COVID-19.

a case for the use of albumin levels as a prognostic marker in these patients.[13] Albumin is a negative acute phase reactant, and the clinical relevance of low albumin as a predictor of outcomes must be interpreted with caution.

Coagulation disturbances

Prothrombin time/international normalized ratio: Coagulation disturbances in COVID-19 may be due to either a dysregulated immune response or liver failure, with dysregulated immune response being more commonly encountered.[30,31] The cytokine storm syndrome (referred to herein as CSS) associated with COVID-19 leads to excessive pro-inflammatory cytokine release, which eventually results in endothelial injury, which may lead to disseminated intravascular coagulation, microvascular thrombotic angiopathy, and pulmonary embolism.[32,33] Several studies have described prolonged prothrombin times and D-dimer levels.[30,34,35]

Endotheliitis was observed in the liver of patients with COVID-19 and fibrin microthrombi were found in liver sinusoids.[36,37] The largest series of liver biopsies taken at autopsy (48 patients) showed massive dilation of portal vein branches, luminal thrombosis, portal tract fibrosis, and microthrombi in the sinusoids.[38]

The altered liver function tests (LFTs) could be related to CSS leading to shock and coagulopathy, affecting liver perfusion and resulting in cell death.[38,39] Klok *et al*.[40] reviewed 184 patients admitted in three intensive care units (ICUs) in the Netherlands and reported the composite incidence of thrombotic events (considering both arterial and/or venous) to be 49 % adjusted for competing risk of mortality. The most common thrombotic event was pulmonary thromboembolism, seen in 87% of patients. Tang *et al*.[41] determined that the administration of low molecular weight heparin (LMWH) for 7 days or longer was associated with lower 28-day mortality in patients with sepsis-induced coagulopathy

Table 1. Prevalence of liver manifestations in patients with COVID-19 as reported in meta-analyses

Author[Ref]	Mao *et al*.[7]	Sultan *et al*.[8]	Parasa *et al*.[9]	Kumar *et al*.[10]	Wan *et al*.[11]	Zarifian *et al*.[12]	Kulkarni *et al*.[13]
Patients included	6,686	10,676	4,805	4,676	15,141	13,251	20,479
Elevated AST	21%	15%	20%	25%	25.4%	22.8%	22.5%
Elevated ALT	18%	15%	14.6%	23%	25.3%	20.6%	20.1%
Elevated Bilirubin	6%	16.7%	NR	9%	8.8%	7.8%	13.4%
Prolonged INR	NR	NR	NR	7%	NR	18%	9.7%
Hypoalbuminemia	6%	NR	NR	60%	NR	39.8%	55.5%
ALP	NR	NR	NR	NR	NR	4.6%	6.1%
GGT	NR	NR	NR	NR	NR	NR	21.1%

INR, international normalized ratio; NR, not reported.

Table 2. Prevalence of GI liver manifestations in patients with COVID-19 infection as reported in individual studies from across the countries to highlight the regional variation

Author[Ref]	Laszkowska *et al*.[14]	Guan *et al*.[15]	Aghemo *et al*.[16]	Moura *et al*.[17]	Docherty *et al*.[18]	Rivera *et al*.[19]
Patients included	2,804	1,099	292	400	20,133	76
Country	USA	China	Italy	Brazil	UK	Spain
Overall prevalence of GI symptoms	38.7%	NR	28.2%	33.4%	29%	59.2%
Diarrhea	23.4%	3.8%	27.1%	17.3%	20.4%	40.8%
Nausea/vomiting	23.2%	5%	4.0%	13.8%	19.8%	22.4%/9.2%
Abdominal pain	11.9%	NR	NR	11.5%	10.2%	27.6%
Anorexia	NR	NR	NR	6%	NR	15.8%
Elevated AST	NR	22.2%	26.7%	NR	NR	NR
Elevated ALT	NR	21.3%	18.5%	NR	NR	NR
Elevated bilirubin	NR	10.5%	10.6%	NR	NR	NR
Prolonged INR	NR	NR	NR	NR	NR	NR
Elevated ALP	NR	NR	9.6%	NR	NR	NR
Hypoalbuminemia	NR	NR	NR	NR	NR	NR

INR, international normalized ratio; NR, Not reported.

(SIC) score of ≥ 4 or a D-dimer value of > 6 times the ULN. They used a working definition of SIC as previously defined by the presence of infection-induced organ dysfunction as characterized using a composite score compiled using platelets, international normalized ratio (INR), and sequential organ failure (SOFA) score.[42]

SARS-CoV-2 and acute liver failure

As noted previously, a non-specific rise in AST and ALT levels up to 5 times the ULN can be seen in COVID-19 patients, along with hyperbilirubinemia. Acute liver failure (ALF) has been reported rarely. Of the five ALF cases reported, three were from the USA and one from Germany and Qatar each.[43–47] Two of these were young, aged 24 years and 35 years, while the other three were above 50 years of age. Most of these patients were critically ill and a single etiology could not be identified as a cause except in the patient with hepatitis B co-infection, who had acute fulminant hepatitis B infection but only mild COVID-19 pneumonia. Out of the five ALF patients, two survived, two expired, and one remained critically ill at the time of writing.

SARS-CoV-2 and hepatitis B

Hepatitis B virus (HBV) infection rates among patients with COVID-19 have been reported between 2.1% and 12.2% from China. Zou *et al*.[48] reported their clinical experience of 20 patients with COVID-19 and chronic HBV co-infection in a retrospective analysis, noting its severe illness and poor prognosis compared to 306 patients with only COVID-19 infection. They reported significantly lower prealbumin levels but no difference in levels of liver enzymes, length of hospital stay or discharge rates. Chen *et al*.,[49] in their retrospective analysis of 123 cases, including 15 cases with HBV, reported more severe disease in HBV-COVID-19 coinfection compared to HBV-negative cases (46.7% vs. 24.1%) as well as a higher mortality rate (13.3% vs. 2.8%). Zha *et al*.,[50] in their observational study of 31 cases, had 2 patients with HBV infection and found that they took a longer time to clear COVID-19 infection (mean difference of 10.6 days). Aldhaleei *et al*.[51] reported a case of hepatitis B flare due to COVID-19, although large-scale studies are required to validate these findings. There is a single case report of HBV induced ALF in a patient with mild SARS-CoV-2 infection.[47]

SARS-CoV-2 and hepatitis C

There is very limited data on hepatitis C virus (HCV) and COVID-19. Wang *et al.*,[52] in their case-control study of over 1 million patients with cirrhosis, included 16,530 with COVID-19 and 820 with COVID-19 and chronic liver disease (CLD) and reported higher odds for patients with HCV in acquiring COVID-19 than for those without [adjusted odds ratio of 12.9]. Thus, although these findings would support the notion that patients with HCV-related CLD are at a greater risk for acquiring COVID-19 infections, there is a dearth of data to validate this finding or identify the impact of COVID-19 on disease course, management and outcome.

SARS-CoV-2 and alcoholic liver disease

No studies have looked exclusively at outcomes of patients with alcoholic liver disease (ALD) with COVID-19. However, a retrospective study from our center reported that the fraction of patients with ALD had decreased in the early part of the pandemic compared to the pre-pandemic era, likely as a result of total lockdown imposed in India and decreased alcohol availability.[53,54] However, the outcome of these patients was not different from those with other etiologies.[53] Following lifting of the lockdown and increased availability and sale of alcohol, a center from the UK reported doubling of admissions due to ALD and an increase in the proportion of patients with severe alcoholic hepatitis and alcohol-related acute-on-chronic liver failure (ACLF).[55]

SARS-CoV-2 and autoimmune liver disease

Data on the impact of COVID-19 on primary biliary cirrho-

sis (PBC), primary sclerosing cholangitis (PSC) or autoimmune hepatitis (AIH) are evolving. Since COVID-19 is associated with transaminitis and hyperbilirubinemia, it may be confused with a flare of AIH. Thus, a liver biopsy may be mandated to confirm the diagnosis prior to initiation of therapy.[56] Gerussi *et al*.,[57] in their case series, described 10 patients across seven hospitals in Italy who were undergoing immunosuppression for AIH. Of the 10 patients, 2 had a recent flare for which they were on high dose steroids. Liver enzymes remained normal in all cases and improved in the two acute cases.

A recently published large retrospective study of 70 patients with AIH, 19 with PBC, 19 with PSC and 16 with variant syndromes were compared in a propensity-matched analysis to 862 non-AIH CLD and 769 patients without liver disease.[58] The cohort with AIH had no increase in ICU stay or mortality compared to patients with other liver disease etiologies or those without liver disease, although close to 80% of AIH patients were on immunosuppression.[58] The only significant factors for AIH mortality were age and baseline liver disease. The authors hypothesized that despite immunosuppression, patients with AIH have preserved immune responses to SARS-CoV-2 and hence are not at a disadvantage. This large study reassures patients and physicians alike and strengthens the already prevalent recommendation of not changing these patients' immunosuppressive therapy in the pandemic.[58]

SARS-CoV-2 and non-alcoholic fatty liver disease

Two large retrospective studies show that presence of non-alcoholic fatty liver disease (NAFLD) is a risk factor for development of severe COVID and mortality even after correcting for comorbidities, such as obesity and diabetes.[59,60] The authors hypothesized that the increased progression of COVID-19 in patients with NAFLD might be due to either exaggerated hepatic immune response contributing to systemic inflammation or the prothrombotic state in these patients contributing to disease progression.[61] However, a third large retrospective study failed to reach similar conclusions, possibly because of different criteria used to define COVID-19 progression and a higher fraction of patients with diabetes (50%) compared to the previous two studies, which might have negated the effect of NAFLD on multivariate analysis.[62]

SARS-CoV-2 and DILI

Although liver injury might occur in patients infected with SARS-CoV-2 due to many reasons, DILI should be considered among the important differentials of liver injury in these patients. The commonly implicated drugs include those which have been repurposed for use in COVID-19, such as hydroxychloroquine (HCQ), azithromycin, lopinavir/ritonavir, baricitinib, and those which been developed exclusively for COVID-19, such as remdesivir. Idiosyncratic DILI is a well-known but rare adverse effect of HCQ.[63] Azithromycin is also associated with rare idiosyncratic cholestatic hepatitis.[63] Lopinavir has been shown to cause both hepatocellular and cholestatic liver injury, leading to enzyme elevation up to > 5-times the ULN in 3% to 10% of patients.[63] The current information on remdesivir suggests that is an unlikely cause of clinically significant liver injury, as suggested by healthy volunteer studies and controlled studies.[64] The safety data on favipiravir, although sparse, appears to be reassuring.[65] Tocilizumab and other interleukin (IL)-6 antagonizing therapies, although frequently associated with elevated aminotransferases (10% to 50%), are rarely associated with elevations > 5-times the ULN (1–2%).[66] Tocilizumab and other immunosuppressants used in the treatment of COVID-19 are also theoretically associated with the risk of reactivation of viral hepatitis.[66] Baricitinib is an unlikely cause of DILI but has been associated with risk of reactivation of hepatitis B.[67]

Acute decompensation and ACLF

Patients with CLD and cirrhosis have systemic immunodeficiency, which places them at a higher risk for COVID-19. Data available from registries place the number of new decompensations at 45% and the mortality rate in such patients at 40%, which is higher in patients with advanced liver disease.[53,68,69] The clinical presentations include acute decompensation-jaundice, ascites, hepatic encephalopathy, and GI bleed.[53,68] Severe presentation includes ACLF with organ failure.

In their multicentric study, Bajaj *et al*.[68] reviewed 37 patients with cirrhosis and COVID-19 compared to a cohort of 127 patients with cirrhosis alone and 108 patients with COVID-19 alone. ACLF, as per North American Consortium for the Study of End-Stage Liver Disease (known as the NACSELD) criteria, was seen in 40 patients, with 11 in the cirrhosis-COVID-19 group and 29 in the COVID-19 group alone and with no difference in mortality across both groups (55% vs. 36%, p=0.25). The authors also reported higher mechanical ventilation and non-invasive ventilation use requirements, central line placement and ICU transfer in the cirrhosis and COVID-19 group compared to the cirrhosis only group. A study from our center compared 28 patients with cirrhosis and COVID-19 with 78 historical controls with cirrhosis matched for etiology and model for end-stage liver disease (commonly referred to as MELD) score. The overall mortality rate was higher in the cirrhosis and COVID-19 group, at 42.3% vs. 23.1%, p=0.07. The mortality was even higher in the sicker group with ACLF and COVID-19, 100% vs. 53.3%, p=0.01.[53]

Variceal bleeding

Although the data on upper gastrointestinal (referred to herein as UGI) bleeding in patients with COVID-19 continues to evolve, there are limited data on variceal bleed in patients with cirrhosis and COVID-19. In a study from our center evaluating the outcomes of cirrhosis in COVID-19 infection, variceal bleeding was the most common form of decompensation present in 11/16 (68%) of the patients.[53] In another study from our center, UGI bleeding was present in 24/1,342 (1.8%) of all patients hospitalized with COVID-19.[70] The majority (88%) of bleeding episodes represented variceal bleeds in patients with cirrhosis and had encouraging outcomes with no rebleed or death at 5 days with primary conservative management.[70]

Hepatocellular carcinoma

The presence of hepatocellular carcinoma (referred to herein as HCC) is associated with poor outcomes, with an increased risk of overall and COVID-19-related mortality in patients with CLD and COVID-19 infection.[71] In addition, the COVID-19 pandemic has also affected the standard of care of patients with HCC. In a large retrospective study, including more than 600 patients, a lower number of patients were evaluated during the pandemic period compared to the same period prior to the pandemic. More than 20% of patients experienced a treatment delay and 13.1% needed

a modification in the treatment strategy, both attributable to the COVID-19 pandemic.[72]

Liver transplant

A multicentric registry reported outcomes of patients with liver transplants (n=151) compared to controls (n=627).[73] GI symptoms (nausea, vomiting, abdominal pain, and diarrhea) were experienced by a greater proportion of patients in the transplant cohort than the comparison cohort- 30% vs. 12%, p<0.001. There was no difference in respiratory symptoms experienced (77% vs. 81%, p=0.248) or hospitalization rates (82% vs. 76%, p=0.106) between the two groups. However, the rates of ICU admission (28% vs. 8%, p<0.001) and the proportion receiving invasive ventilation (20% vs. 5%) were higher, and median hospital stay (11 days vs. 8 days, p=0.046) was longer in the liver transplant group. Surprisingly, the proportion of deaths in the transplant cohort was significantly less than the comparison cohort (19% vs. 27%, p=0.046) with the dominant cause of death being COVID-19 lung disease. The authors also reported no liver-related mortality, rejection, or re-transplant in the transplant group. Similar outcomes have been reported from a prospective study from Spain (18%) and UK national registries (20%).[73,74] The Spanish study reported on the prospective follow-up of 111 post-transplant recipients and showed that although chronically immunosuppressed patients are at increased risk of acquiring the infection yet, they are not at increased risk of mortality.[74] The analysis also reported no effect on immunosuppression on mortality, particularly calcineurin inhibitors and mammalian target of rapamycin (commonly known as mTOR) inhibitors, except mycophenolate, particularly in doses greater than 1 g per day (relative risk of 3.94).[74] The authors hypothesize that this effect might be due to the CD8+ depleting effect of mycophenolate.[74]

SARS-CoV-2 cholangiopathy

ACE-2 receptor and TMPRSS2 are highly expressed on cholangiocytes, and hepatic organoid models have been used to show the virus's direct cytopathic effect on cholangiocytes.[4] Recently, a small case series described an entity called post-COVID-19 cholangiopathy that is characterized by changes in both extrahepatic and intrahepatic biliary tree with microscopic features of severe vacuolization injury to cholangiocytes, along with microangiopathy and evidence of developing secondary biliary cirrhosis among three patients who initially had severe elevation of liver enzymes and acute hypoxemic respiratory failure, and prolonged hospitalization due to COVID.[75] However, the exact contribution of SARS-CoV-2 in the development of cholangiopathy is unclear, since a similar entity has been demonstrated in critically ill hospitalized patients. None of the patients in the above series had immunohistochemical evidence of SARS-CoV-2 infection on liver biopsy samples.[76]

Gallbladder

Few case reports exist which describe patients presenting with COVID-19 and acute cholecystitis with the disease attributed to the virus on the basis of positive quantitative reverse transcription-polymerase chain reaction (referred to herein as RT-PCR) of tissue samples in one patient, while the other two had positive RT-PCR results for nasopharyngeal swabs.[77–79] All three patients had acalculous cholecystitis with positive Murphy's sign, thickening of gallbladder wall and pericholecystic fluid on ultrasound. However, the significance of these findings in the pathogenesis of COVID-19 needs to be elucidated.

Evaluation of patients with liver manifestations of COVID-19

Patients presenting with acute febrile illness and respiratory symptoms, such as sore throat, nasal stuffiness, dry cough and breathlessness, should undoubtedly be evaluated for COVID-19. Patients presenting with transaminitis, either symptomatic or asymptomatic, should also be offered testing for COVID-19 apart from standard tests for viral hepatitis, autoimmune markers, copper studies and metabolic panel. Similarly, patients with underlying liver disease presenting with new decompensation or ACLF should also be tested for COVID-19.[53]

Despite the ongoing pandemic, the scourge of tropical diseases, such as dengue, malaria, chikungunya, typhoid, tuberculosis, and scrub typhus, should not be forgotten, as they may share certain symptoms with COVID-19 but treatment and prognosis differ. Moreover, co-infections with COVID-19 and these tropical illnesses have been frequently reported.[20–22] Hence, in patients presenting with acute febrile illness, these differentials should also be considered, apart from COVID-19.

Management of patients with liver manifestations

Management of GI symptoms does not require specific drugs, apart from those approved for management of COVID-19, which are in a state of continuous evolution. Transaminitis should trigger a search for reversible and alternate causes of liver injury along with a diligent search for a culprit drug among the drugs the patient is receiving. Management of patients with decompensated liver disease and ACLF should be done according to standard guidelines.[80] Patients with variceal bleed may require endoscopy, which should be done with all recommended precautions, including personal protective equipment, preferably in a negative pressure room.[81]

Lack of knowledge in the current literature

The GI and liver manifestations of COVID-19 have been described now in multiple studies. The clinical implications of the new strain of COVID-19, the VOC 202012/01 strain known to spread faster, need to be seen.[82] The effect of this new strain on hepatic manifestations remains to be explored. Emerging data also suggest that immunity to COVID-19 infection wanes rapidly, particularly in asymptomatic individuals.[83] In light of these findings, reinfection has also been reported.[84] Whether reinfection tends to be asymptomatic or presents with more severe hepatic manifestations remains to be seen.

Conclusion and points to focus on in future studies

A year or so into the COVID-19 pandemic, we have learned that liver involvement is common, but usually secondary, and seen more commonly in severe COVID-19.[13] The speculated mechanisms for hepatic injury, in addition to direct viral cytotoxicity, are immune injury, cytokine storm, ischemia and hypoxia reperfusion injury.[5] We need more studies to unravel the mystery of pathogenesis of liver involvement

in COVID-19. Multiple therapies have been recommended in COVID-19, with different efficacies and side effect profiles. The therapeutic armamentarium against COVID-19 is rapidly expanding but with modest evidence for the efficacy of remdesivir and dexamethasone in moderate to severe COVID-19.[85] Most drug trials have excluded patients with underlying CLD and GI disease. What needs to be looked at is the effect of these drugs on patients of cirrhosis and ACLF, where the immune system is already dysregulated. Vaccination has already started in North America, Europe and India, with many more vaccines still in preclinical development and some in clinical trials.[86] Vaccination forms the basis of exit strategy in this pandemic to return back to normal lives. There have been doubts about the duration of natural immunity in COVID-19 and speculation that vaccine-induced immunity will last longer. We need to study how long the immune response lasts in patients with liver disease, immune response generation to vaccines in these patients and what type of vaccine would be best suited for special populations, as different vaccines would have different storage requirements, cost, adverse effect profiles and efficacies.[87]

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (S), acquisition of data (AE, MV, SB, AC, AA, S), analysis and interpretation of data (AE, MV, SB, AC, AA, S), drafting of the manuscript (AE, MV, SB, AC, AA, S), critical revision of the manuscript for important intellectual content (AA, AC, S), administrative, technical, or material support, study supervision (S)

Data sharing statement

All data are available upon request.

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