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MINIREVIEWS

Liver injury in COVID-19: The hepatic aspect of the respiratory syndrome — what we know so far

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Abstract

The 2019 novel coronavirus disease (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a serious threat to global public health. Although primarily, the infection causes lung injury, liver enzyme abnormalities have also been reported to occur during the course of the disease. We conducted an extensive literature review using the PubMed database on articles covering a broad range of issues related to COVID-19 and hepatic injury. The present review summarizes available information on the spectrum of liver involvement, the possible mechanisms and risk factors of liver injury due to SARS-CoV-2 infection, and the prognostic significance of the presence of liver injury. Hopefully, this review will enable clinicians, especially the hepatologists, to understand and manage the liver derangements they may encounter in these patients better and provide guidance for further studies on the liver injury of COVID-19.

Key Words: COVID-19; Hepatitis; Infectious disease; Liver injury; SARS-CoV-2; Management

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Core Tip: Hepatic injury in coronavirus disease 2019 (COVID-19) has been widely observed. Although the pathogenic mechanisms still remain unclear, it is believed to be due to interplay of multiple factors. In this review, we have tried to discuss the pathophysiological mechanisms of hepatic injury in the context of COVID-19 and have proposed a management outline of such injury.

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INTRODUCTION

An outbreak of novel corona virus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) infection occurred in Hubei province of Wuhan, China in December, 2019 and since then it has assumed the form of a pandemic spanning 213 countries with more than 26.3 million confirmed cases worldwide and causing 869000 deaths as of September 3, 2020[1]. The syndrome caused by the virus SARS-CoV-2 has been named coronavirus disease 2019 (COVID-19). The virus can cause an acute respiratory illness which resolves quickly but may also lead to massive alveolar damage with respiratory failure. Although the presenting complaints are chiefly respiratory, the gastrointestinal system and the liver, in particular have also been found to be affected[2]. This is evident in a large series of 5700 cases from New York where the authors reported liver enzymes abnormalities in more than half of the cases[3].

CLINICAL PROFILE OF PATIENTS OF COVID-19

SARS-CoV-2 primarily causes a respiratory syndrome heralded by fever, myalgia, sore throat, runny nose and dyspnea in severe cases. COVID-19 has been reported to have a slight male predilection of around 73% and a median age of presentation of 49 years[4]. Amongst other atypical symptoms, diarrhea has also been reported to occur as a presenting complaint in the absence of respiratory symptoms. What is also concerning is that 32% of the patients required intensive care unit (ICU) admission, of which 15% expired. Another study reported by Wang *et al*[5] that included 138 patients also reported similar clinical characteristics. It has also been reported that many of the patients belonging to the elderly age group who become severely ill have evidence of underlying illness such as cardiovascular disease, liver disease, kidney disease, or malignancies[3].

A significant proportion of the patients with COVID-19 have also been found to have a number of digestive disorders like anorexia, nausea, vomiting, diarrhea and abdominal pain[6]. The involvement of the gastrointestinal system, and the hepatobiliary system in particular, is significant in view of the fact that the case studies and data from The Fifth Medical Centre of PLS General Hospital, Beijing, China indicate that 2%-11% of patients with COVID-19 had liver comorbidities and 14%-53% cases reported abnormal levels of alanine aminotransferase and aspartate aminotransferase (AST) during disease progression[2]. Also, it was observed that the synthetic function of the liver was affected, being evident in the fact that prothrombin time prolongation was more significant in patients with digestive symptoms[6].

CORONAVIRUSES AND LIVER INJURY

Similar to the current pandemic, studies had showed that liver injury also occurred in patients with SARS-which broke out two decades ago—manifesting mainly as transaminitis along with increases in serum bilirubin and decreased serum albumin[7].

It was found that, apart from causing alveolar injury, SARS also caused direct hepatocyte injury by using angiotensin converting enzyme 2 (ACE2) receptor for

cellular entry, which is abundantly expressed in the liver[8]. Further confirmation of this came from reverse transcription polymerase chain reaction (RT-PCR) based evidence of SARS-associated coronavirus in the liver tissues despite electron microscopy failing to identify viral particles[9].

Similarly, Middle East respiratory syndrome (MERS) caused by Middle East respiratory syndrome coronavirus (MERS-CoV) was characterised by fever, which also progressed to respiratory and multiorgan failure, in severe cases. These patients also had hyperbilirubinemia, hypoalbuminemia and transaminitis. In contrast to the SARS-CoV, MERS-CoV was found to have specific affinity for the Dipeptidyl Peptidase-4 (DPP-4) receptor which is abundantly expressed in the liver and thus was presumed to have gained entry into hepatocytes[10]. In this case, too, viral particles could not be demonstrated in the liver tissue of patients with MERS[11].

In a study involving 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in China, nausea or vomiting, or both, and diarrhoea were reported in 55 (5.6%) and 42 (3.8%) patients respectively[12]. Interestingly, SARS-CoV-2 RNA was first detected in a stool specimen of the first reported COVID-19 case in the United States[13].

It has been shown that SARS-CoV-2 shares 82% genomic sequence similarity with SARS-CoV and has also been found to have affinity for the ACE2 receptor[6,14]. Therefore, it is not at all surprising that 14%-53% of patients with COVID-19 have abnormalities in transaminase levels[2]. In the past too, liver impairment was reported in 60% of patients with SARS[9,15].

Liver dysfunction in COVID-19 is manifested by abnormal transaminase levels and this has also been linked to the severity of the disease as well as the outcome. For example, in one study published by Huang *et al*[4], elevation of AST was observed in eight (62%) of 13 patients in the ICU compared with seven (25%) of 28 patients who did not require care in the ICU. In another comparatively bigger cohort of 1099 patients from 552 hospitals in 31 provinces in China, patients with more severe disease had abnormal liver aminotransferase levels than did patients with less severe disease[12]. In one more study, 8 patients who had a diagnosis of COVID-19 confirmed by computed tomography (CT) scan while in the asymptomatic phase had significantly lower incidence of AST abnormality compared to patients diagnosed after the onset of symptoms[16]. All these figures indicate that liver injury manifested by transaminitis is probably more prevalent in severe cases than in mild cases of COVID-19.

RISK FACTORS FOR LIVER INJURY

There are not many studies addressing the risk factors associated with liver injury in COVID-19. It is quite natural that a thorough and comprehensive evaluation of possible risk factors that can cause or exacerbate liver injury has not been possible in such a short span of time.

An important observation in a study by Li *et al*[17] was that among patients with abnormal liver function, patients with moderate and severe disease were more likely to have liver injury, accounting for 58.8% and 66.7% respectively. This indicates that hepatic injury is more common and is more severe during the period of critical care, where the patient is exposed to multiple insults in the form of medications, hemodynamic instability and cytokine storm. This is in addition to the fact that a significant number of patients in China have underlying hepatitis B infection.

The authors, in the same study, performed multivariate logistic regression analysis to study the association of several factors that included age, drinking history, baseline albumin, lactic acid, C-reactive protein (CRP), neutrophils, lymphocyte and myoglobin. It was found that CRP levels greater than 20 mg/L and a lymphocyte count less than 1.1×10^9/L were independently related to alanine aminotransferase (ALT) elevation. This study, importantly, excluded the effects of drugs that might cause hepatic injury and suggested that cytokine storm may be the major mechanism behind lymphopenia and elevation in CRP, heralding liver injury.

In addition, herbal medicines, which are a major cause of liver injury in the developing nations[18], complicate the problem further as they have been indiscriminately used in these cases in China. A dataset processed by Ou *et al*[19] from between 2011 and 2014 in China identified Chinese herbal medicine as the primary cause of liver injury in 36% of the patients investigated in their study. Therefore, in such a background of widespread consumption of herbal products which is an established risk factor for liver injury, patients with COVID-19 seem to be at high risk for exacerbation of hepatic injury due to a combination of multiple factors.

PATHOGENESIS OF LIVER INJURY

As discussed earlier, it has been observed that SARS-CoV-2, by virtue of its affinity for ACE2 receptor gains access to hepatocytes and causes direct liver injury. However, what is puzzling is that the ACE2 expression of bile duct cells is reportedly much higher than that of liver cells, and is comparable to alveolar type 2 cells in the lungs[20]. As bile duct epithelial cells are known to play important roles in liver regeneration and immune response[21], it is believed that the liver injury in COVID-19 patients may be due to the damage to bile duct cells by the virus, and not the liver cells, and in such a scenario, it would be expected that COVID-19 patients should have evidence of cholestatic liver injury. However, the normal ALP levels and elevated AST/ALT levels do not favour the injury hypothesis, and our understanding with regards to liver injury related to SARs-CoV-2 continues to evolve. Besides, histopathological analysis of liver tissue from a deceased patient also did not show the presence of viral inclusion bodies in the liver[22].

It is in this context that other factors apart from direct viral cytopathic injury need to be considered. In addition to direct hepatotoxicity, it is clear that immune dysregulation does occur in COVID-19 in varying forms. Systemic Inflammatory Response Syndrome (SIRS) and accompanying release of interleukins and other mediators of inflammation lead to a form of cytokine storm that can cause and exacerbate hepatocellular injury[23]. Furthermore, a metanalytic study investigating the relationship between liver damage and COVID-19 suggests that SARS-CoV-2 may produce a relevant hepatic damage probably through the immune interactions requiring the action of intrahepatic cytotoxic T cells and Kupffer cells[24].

Another factor that needs to be kept in mind while dealing with hepatic dysfunction in COVID-19 is the possibility of pneumonitis associated hypoxia and fall in mean arterial pressure that can cause ischemic hepatitis. Besides, the fact that patients in ICU had higher levels of transaminases might also be due to the higher degrees of hypoxia requiring mechanical ventilation. Levels of AST and ALT in thousands are an established feature of ischemic hepatitis, and hypoxia may in fact exacerbate the liver injury along with other causes of liver dysfunction.

Drug induced liver injury during COVID-19 related illness should be considered in the differential diagnosis considering many of the unapproved drugs are being tested either empirically or are undergoing clinical trials. While there is no specific treatment for COVID-19 till date, there has been a frenetic attempt to use various existing combinations of antivirals, immunomodulators, antibiotics and steroids in addition to 'hepatoprotective' drugs. The indiscriminate use of such cocktails might, in fact, be perpetuating hepatic dysfunction observed in these cases. Biopsies performed post mortem in SARS-CoV-2 infection revealed microvascular steatosis and mild lobular and portal activity, indicating that the injury could have been caused by drug-induced liver injury in addition to the SARS-CoV-2 infection[23]. Use of steroids, antibiotics and antivirals have all been associated with liver injury. It has also been reported that the liver injury observed in COVID-19 patients might be caused by lopinavir/ritonavir, which is being used as an antiviral for the treatment of SARS -CoV-2 infection[25]. The drug Remdesivir, widely used in COVID-19, has been reported to cause hepatocellular injury and derangement of liver function[26,27]. Use of biologics like Tocilizumab has been associated with Hepatitis B reactivation[28]. Azithromycin which is commonly prescribed in COVID-19 is a known cause of idiosyncratic liver injury while hydroxychloroquine may also rarely cause idiosyncratic hepatotoxicity[29,30]. Therefore, it is amply clear that the sheer number of medications being tried in COVID-19 is highly likely to cause liver injury ranging from asymptomatic transaminitis to greater degrees of hepatotoxicity. The APASL expert panel consensus recommendations advise careful investigation of drug induced liver injury in COVID-19 and specifically mention against using certain drugs like Remdesivir in patients with decompensated chronic liver disease and ALT elevations more than 5 times the upper limit of normal[27]. Close monitoring of liver function tests has been advised. In addition, it has also been suggested that use of herbal products and nutraceuticals in COVID-19 may interfere with the body's natural immune mechanisms and hence the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) has advised against using these substances derived from plants like poplar, birch, willow, goldenrod, curcuma *etc*.[31,32]. A summary of the spectrum of drugs used in COVID-19 likely to induce liver injury is shown in Figure 1.

To add to this growing concern over liver injury in COVID-19, the presence of chronic liver disease adds to the burden of the problem worldwide. The prevalence of liver disease varies globally and so do the etiologies. Viral hepatitis, alcohol related liver disease and non-alcoholic fatty liver disease are prevalent in epidemic

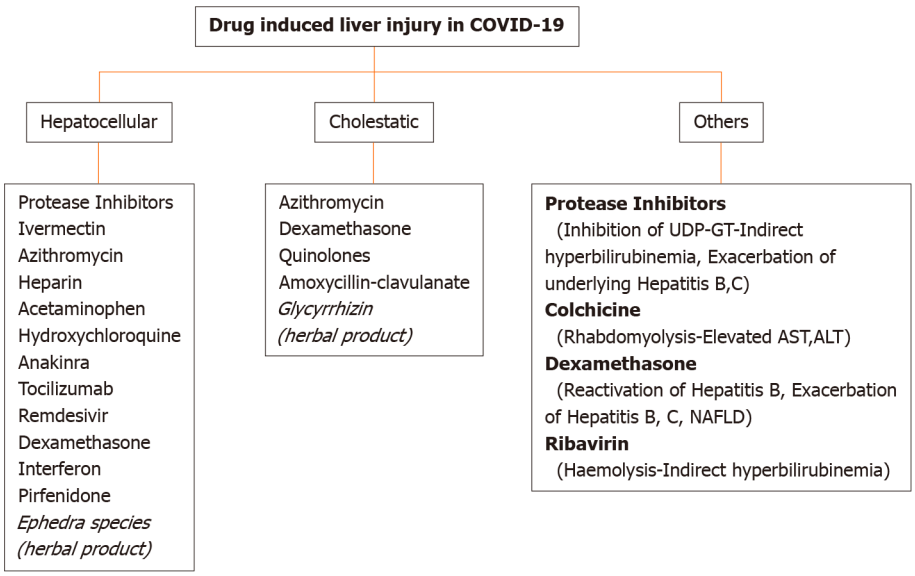

Figure 1 Spectrum of medications used in coronavirus disease 2019 likely to cause liver injury. COVID-19: Coronavirus disease 2019; UDP-GT: UDP-glucuronosyltransferase; NAFLD: Nonalcoholic fatty liver disease.

proportions worldwide and the impact of COVID-19 in patients with these pre-existing diseases is largely unknown. A recent case series from China reported that decompensated cirrhosis may be a risk factor for a poor outcome in patients with COVID-19[33]. The use of complementary, herbal and indigenous drugs that can exacerbate liver injury, especially in countries like China where the infection originated and in India, where the incidence of new cases has been steadily rising - poses great challenges.

The presence of co-morbidities makes the pathogenic processes complex and at the moment, there are very few studies that have looked at this problem. A systematic review and meta-analysis by Yang *et al*[34] has shown that the most prevalent comorbidities were hypertension and diabetes, followed by cardiovascular diseases and respiratory system disease. It is well known that both hypertension and diabetes are commonly treated with ACE inhibitors. The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). This results in an upregulation of ACE2. Consequently, it has been hypothesised that the increased expression of ACE2 in different organs like the lung and the liver might facilitate infection with SARS-CoV-2. Thus, it has been assumed that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19[26]. Further, these studies suggest that patients with co-morbidities having SARS-CoV-2 infection might have multiple pathogenic mechanisms of host injury and inflammatory response proceeding simultaneously. Given the high burden of co-morbidities, especially among the elderly population, this area needs to be meticulously investigated. The potential mechanisms of liver injury in COVID 19 are summarized in Figure 2.

PATTERN OF LIVER INJURY IN SARS-COV-2 INFECTION

Liver injury in SARS-CoV-2 infection has a variable incidence of 14%-53% as indicated by elevated AST and ALT levels. There is also an accompanying mild increase of serum bilirubin levels[35]. However, from the existing data, the pattern of bilirubin rise (direct *vs* indirect) and its relationship to the disease process is not very clear. Also, no correlation between the rise in transaminases and bilirubin levels have been found. Hypoalbuminemia has also been found to occur with the serum albumin levels around 2.63-3.09 mg/dL according to one study[4]. A recent study including 417 patients with COVID-19, 318 (76.3%) had abnormal liver test results and 90 (21.5%) had liver injury during the hospitalization. Ninety-one (21.8%) developed severe disease and 326 (78.2%) had mild disease during hospitalization (Figure 2) [36]. A recent study has noted that AST-dominant aminotransferase elevation is common in COVID-19, mirrors

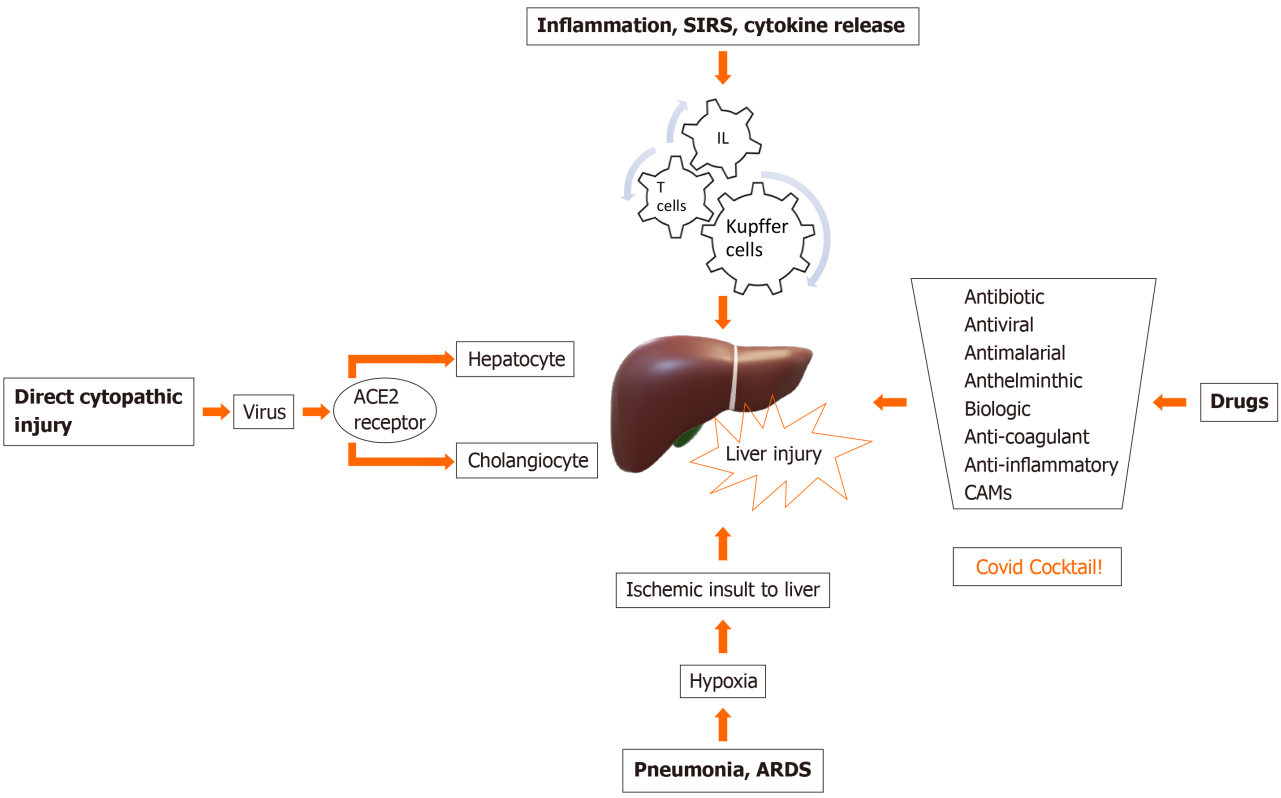

Figure 2 Potential mechanisms of liver injury in coronavirus disease 2019. ACE2: Angiotensin converting enzyme 2; ARDS: Acute respiratory distress syndrome; CAMs: Complementary and alternative medicines; IL: Interleukin.

disease severity, and appears to reflect true hepatic injury[37].

Interestingly, COVID-19 infection presenting as acute non-icteric hepatitis which preceded the development of fever and respiratory symptoms has recently been reported in a patient[38]. This particular case report assumes importance in view of the fact that the patient did not have typical features of COVID 19 at presentation and was worked up as a case of acute viral hepatitis. All possible causes of acute hepatitis were ruled out. After 2 d, she developed respiratory signs and symptoms and was found positive for SARS CoV-2. She responded to treatment with supportive measures and hydroxychloroquine[38]. Furthermore, a case of COVID-19 hepatitis in a living donor liver allograft recipient whose donor subsequently tested positive for COVID-19 has been reported with unique histopathological findings[39].

The proportion of patients developing liver injury in severe COVID-19 has been found to be significantly higher than that in patients with milder disease. In a metanalytic study by Mantovani *et al*[24], patients with severe COVID-19 disease tended to have higher levels of liver enzymes, as well as a greater activation of coagulative and fibrinolytic pathways. While the elevation in AST and ALT have been around three to four times and has varied across studies, one study reported elevations in AST and ALT to be in the range of thousands. In another study, although serum gamma glutamyl transpeptidase (GGT) was found to be increased in severe cases, serum alkaline phosphatase (ALP) level was in the normal range in both mild and severe cases[20]. Table 1 summarizes the pattern of liver dysfunction in COVID 19 patients reported in various studies[35,40-70].

SARS-COV-2 INFECTION IN THE SETTING OF PRE-EXISTING LIVER DISEASE

Patients with pre-existing chronic liver disease have a wide spectrum of immune dysfunction starting from cytopenia to cytokine storm. The proportion of COVID-19 patients with pre-existing liver conditions ranged from 2% to 11% in one study[2]. In patients with chronic hepatitis B and C infection, it is not known as to what kind of effect co-infection with SARS-CoV-2 might have. Such patients who remain as inactive

Table 1 Summary of the pattern of liver injury reported in coronavirus disease 2019 in various studies

Ref.	Number of patients	Pattern of liver injury	Pre-existing liver diseases	Comments	Place of study
Richardson *et al*[3]	5700	Elevated AST: 58.4%; elevated ALT: 39%	Cirrhosis: 0.4%; chronic hepatitis B: 0.1%; chronic hepatitis C: 0.1%		Northwell Health System, New York, United States
Huang *et al*[4]	41	15(31%)	1 (2%)	Elevated AST observed in 62% of patients in ICU compared with only 25% of patients not in ICU	Wuhan, China
Wang *et al*[5]	138	Mild elevation of AST and ALT	4 (2.9%)	-	Wuhan, China
Guan *et al*[12]	1099	Elevated AST: 22.2%; elevated ALT: 21.3%; elevated total bilirubin: 10.5%	23 (2.3%)	AST elevated in 18.2% of non-severe disease but in 39.4% of severe disease; ALT elevated in 19.8% with non-severe disease and 28.1% of severe disease	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China
Shi *et al*[16]	81	Transaminitis in 43 (53.1%)	7 (8.6%)	Patients with subclinical infection had lower AST	Wuhan, China
Fan *et al*[25]	148	Abnormal LFT in 50.7%; elevated ALT in 18.2%; elevated AST in 21.6%		Higher proportion (56.1%) with liver injury received lopinavir/ ritonavir than those without liver injury (25%)	Shanghai Public health Clinical Centre, China
Chen *et al*[35]	99	43(43%); elevated AST: 35%; elevated ALT: 28%; elevated total bilirubin: 98%		One patient had severe liver injury with ALT 7590U/L	Wuhan, China
Cai *et al*[36]	417	During hospitalisation, rise in liver enzymes > 3 times of upper limit seen; elevated ALT: 49 (23.4%); elevated AST: 31 (14.8%); elevated total bilirubin: 24 (11.5%); elevated GGT: 51 (24.4%)		318 (76.3%) had abnormal liver biochemistries and 90 (21.5%) had liver injury during hospitalization; 91 (21.8%) developed severe disease and 326 (78.2%) had mild disease during hospitalization; use of lopinavir/ritonavir increased the odds of liver injury by 7-fold	Shenzhen, China
Tabata *et al*[40]	104	Elevated AST: 17.3%; elevated ALT: 16.3%	-	-	Diamond Princess Cruise, Japan
Huang *et al*[41]	36	Elevated ALT: 13.33%; elevated AST: 58.06%; elevated Total bilirubin: 12.90%		All fatal cases only	Wuhan, China
Zhang *et al*[42]	82	Liver dysfunction in 64 (78%)	2 (2.4%)	All fatal cases only	Wuhan, China
Yang *et al*[43]	52	15 (29%)		No difference in incidence of liver injury between survivors and non-survivors	Wuhan, China
Cao *et al*[44]	128			Transaminitis present only in severe disease	Xiangyang, China
Xu *et al*[45]	62	Elevated AST in only 16.1%	7 (11.0%)	No patient had elevated ALT while a sixth had elevated AST	Zhejiang Province, China
Cai *et al*[46]	298	44 (14.8%)	8 (2.7%)	Transaminitis 4 times commoner in severe disease (36.2%) compared to mild disease (9.6%)	Shenzhen, China
Kujawski *et al*[47]	12	Elevated AST: 58.3%; elevated ALT: 58.3%	8.3% had HBV and 8.3% had fatty liver disease		Center of Disease Control California, Illinois, Arizona, Massachusetts,Washington, Wisconsin,

					United States
Arentz *et al*[48]	21	Median AST: 273 (range 14-4432); median ALT: 108 (range 11-1414)	4.8% had cirrhosis of liver		Kirkland, Washington, United States
Jin *et al*[49]	651	Liver injury seen in 13 out of 74 with GI symptoms vs 51 out of 577 without GI symptoms		Rate of increased AST, but not ALT, was significantly higher in patients with GI symptoms than in those without GI symptoms	Zhejiang Province, China
Qi *et al*[50]	267	Elevated AST: 7.2%; elevated ALT: 7.5%; elevated bilirubin: 2.2%		Elevated AST seen in 9 out of 217 patients with non-severe disease and 10 out of 50 patients with severe disease.Elevated ALT seen in 10 out of 217 patients with non-severe disease and 10 out of 50 patients with severe disease.Elevated bilirubin in 3 out of 217 patients with non-severe disease and 3 out of 50 patients with severe disease	Chongqing, China
Omrani-Nava *et al*[51]	93	Elevated AST: 29.2%; elevated ALT: 30.3%; elevated ALP: 17%; elevated total bilirubin: 10.2%; elevated direct bilirubin: 45.8%		Risk of being transferred to the intensive care unit strongly associated with the elevated levels of AST and direct bilirubin	Sari, Amol, Mazandaran Province, Iran
Mao *et al*[52]	214	Median AST 26 (8-8191); median ALT 26 (5-1933)		Liver enzymes were significantly higher in severe cases compared to non-severe cases	Wuhan, China
Xu *et al*[53]	45	Elevated AST/ALT: 37.8%; median Bilirubin: 0.91 (IQR 0.61-1.3)			
Tian *et al*[54]	24	Elevated AST: 8.33 %; elevated ALT: 4.17 %	4.17 % had cirrhosis		Shandong, China
Chen *et al*[55]	291	Elevated AST: 15.1%; elevated ALT: 10.3%; elevated bilirubin: 9.3%	5.2% chronic liver disease	Elevated AST in 5 out of 29 cases in mild illness, 23 out of 212 cases in moderate illness and 16 out of 50 cases in critically ill. Elevated ALT in 4 out of 29 in mild illness, 16 out of 212 cases in moderately ill and 10 out of 50 cases in critically ill. Elevated bilirubin in 4 out of 29 cases in mild illness, 17 out of 212 in moderately ill and 6 out of 50 in critically ill	Hunan Province, China
Wang *et al*[56]	18	Elevated AST or ALT in 25%			Zhengzhou, Henan Province, China
Yan *et al*[57]	168	Elevated AST: 17.3%; elevated ALT: 8.0%		Elevated AST seen in 7 out of 75 patients with non-severe disease and 11 out of 29 patients with severe disease; Elevated ALT seen in 5 out of 81patients with severe disease and 4 out of 31 patients with severe disease	Hainan, China
Lin *et al*[58]	95	Elevated AST: 4.2%; elevated ALT: 5.3%			Zhuhai, Guangdong Province, China
Zhao *et al*[59]	77	Elevated AST: 26.0%; elevated ALT: 33.8%		Elevated AST seen in 11 out of 57 non severe patients and 9 out of 20 severe patients; Elevated ALT seen in 17 out of 57 patients with non-severe disease and 9 out of 20 patients with severe disease	Beijing, China
Chen *et al*[60]	274	Elevated AST: 30.7%; elevated ALT: 21.9%; median bilirubin: 0.6 (IQR 0.4-0.8)	4 % were HbsAg positive		Wuhan, China
Rubin *et al*[61]	54	Elevated AST: 42.59%; elevated ALT: 40.7%	1.8 % were HBV infected	AST: mean/SD-73.4 ± 61.8 (females); 45.1 ± 19.5 (males) ALT: mean/SD- 69.6 ± 65.2 (females); 43.9 ± 25.8 (males)	Stanford University School of Medicine, California
Cholankeril *et al*[62]	116	Deranged LFT in 26 out of 65 cases (40%). Higher levels of AST compared to ALT. Median bilirubin- 0.4 (IQR 0.3-0.7)	2.6% chronic liver disease	22 of the 26 patientswith liver enzyme elevations had normal baseline liver enzymes	Stanford University HospitalsCalifornia, United States
Yao *et al*[63]	40	Elevated AST: 40%; elevated ALT: 52.5% Elevated Bilirubin: 25%		Out of 22 critical cases, 17 had hepatic dysfunction. Out of 18 noncritical cases, 5 had hepatic dysfunction	Xi'an, Shaanxi Province, China

Zhao *et al*[64]	75	Elevated AST: 18.7%; elevated ALT: 20%; elevated Bilirubin: 16%	5.3 % had chronic liver disease		Hefei, Anhui Province, China
Ai *et al*[65]	102	Elevated AST: 25.5%; elevated ALT: 19.6%			Xiangyang, China
Ma *et al*[66]	81	Deranged AST/ALT: 38.2%			Wuhan, China
Xu *et al*[67]	355	Elevated AST: 28.7%; elevated ALT: 25.6%; elevated Total bilirubin: 18.6%			Wuhan, China
Shi *et al*[68]	416	Median AST: 30 (IQR 22-43); median ALT: 28 (IQR 18-46)	1% had HBV infection		Wuhan, China
Luo *et al*[69]	1141	Among 183 patients, median AST: 65.8 ± 12.7, median ALT: 66.4 ± 13.2			Wuhan, China
Qi *et al*[70]	21	Elevated AST: 38.1%; elevated ALT: 23.8%; elevated GGT: 23.8%	All patients	Most common etiology of chronic liver disease was chronic hepatitis B infection	16 designated hospitals in China

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyl transpeptidase; IQR: Interquartile range; HBV: Hepatitis B virus; LEF: Liver function tests; GI: Gastrointestinal; ICU: Intensive care unit; SD: Standard deviation.

carriers or in the immunotolerant phase might have reactivation of the virus and hepatic injury. Mantovani *et al*[24], in their metanalytic study, have suggested that patients with pre-existing chronic liver disease may be more susceptible to liver damage from SARS-CoV-2. Implications of underlying non-alcoholic fatty liver disease (NAFLD) has been recently evaluated. The authors have noted that patients with NAFLD had higher risk of disease progression [6.6% (5/126) *vs* 44.7% (34/76), $P < 0.0001$], higher likelihood of abnormal liver function from admission to discharge[70% (53/76) *vs* 11.1% (14/126), $P < 0.0001$] and longer viral shedding time(17.5 ± 5.2 d *vs* 12.1 ± 4.4 d, $P < 0.0001$) when compared with non-NAFLD subjects[71]. Patients with autoimmune hepatitis and primary biliary cholangitis on steroids and other immunosuppressive therapy might be at higher risk of developing severe disease and may pose dilemma in treatment, considering the fact that use of medications like antivirals and antibiotics might worsen liver injury. This issue also requires further investigation. An interesting case series of three patients of COVID-19 with chronic liver disease showed that while two of the patients with Child-Pugh C disease died, the patient with Child-Pugh class B did not[33]. In addition, the patient with the highest Model for End-stage Liver Disease (MELD) score survived compared to the ones with lower MELD scores who did not, possibly indicating that clinical decompensating events may be more important in predicting outcome of patients with COVID-19 and pre-existing cirrhosis[33].

In a multicentric study in China evaluating the clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis, most patients were found to have compensated cirrhosis while chronic HBV infection was found to be the most common aetiology[70]. The study did not report any significant differences between

survivors and non-survivors in terms of age, sex, comorbidities, aetiology of cirrhosis, Child-Pugh class, MELD score, interval between onset and admission, or onset symptoms of COVID-19[70]. Further, COVID-19 patients who died had lower total lymphocyte and platelet counts, and higher direct bilirubin levels than patients who survived, while the frequency of acute respiratory distress syndrome (ARDS) and gastrointestinal (GI) bleeding were higher in non-survivors compared to survivors[70]. Importantly, the cause of death in most patients was respiratory failure rather than acute on chronic liver failure[70]. Further studies need to be carried out across different population groups to determine the exact impact of SARS-CoV-2 co-infection in patients with chronic liver disease.

SARS-COV-2 INFECTION IN THE SETTING OF LIVER TRANSPLANTATION

Taking a cue from the previous SARS outbreak of 2002, it has been hypothesised that liver transplantation might involve a risk of transmission of viral infection from donor to recipient. Hence, donor screening and testing might prove to be extremely crucial[72]. However, at this juncture, there is a lack of evidence to justify this hypothesis. A case series of patients with COVID-19 had several patients with various comorbidities, but none of them had been a transplant recipient[12]. A recent study from Italy reported experience from a single transplant centre, and noted 3 deaths out of their 111 Long-term liver transplant survivors (transplanted more than 10 years ago) compared to none of the three infected withSARS-CoV-2 transplanted within the last 2 years. All three who died were male, older than 65 years, receiving antihypertensive drugs, overweight (body mass index > 28 kg/m^2), with hyperlipidaemia, and diabetes (median Hemoglobin A1c of 6.9%)[73]. In the present circumstances, in the event of a liver transplantation, the hepatologists have to follow the guidance issued by the Transplantation Society[74], as well as local health department guidelines for isolating, quarantining, testing, and monitoring returned travellers from endemic areas. Recent AASLD guidance reports that there is a significant false negative rate and transplant programs should consider symptoms of COVID-19 to be strongly suggestive of infection despite negative testing. Transplantation in SARS-CoV-2-positive recipients is currently not recommended.

PREVENTION AND TREATMENT

Liver injury in COVID-19 infection can be fleeting and mild and enzyme levels can normalise spontaneously. As of now, there is no specific therapy for liver injury in COVID-19 infection. In addition to managing the respiratory syndrome in COVID-19, monitoring of the liver function tests (LFT) should be done and all factors known to cause or exacerbate liver injury should be taken into consideration while treating the patient. A proper history especially with regard to recent or long-term intake of herbal preparations and hepatotoxic drugs must be taken. Drugs known to cause liver injury must be used with caution and LFT should be repeated at regular intervals. All the studies concerning COVID 19 and liver injury are from China and one thing common in these studies is the use of a cocktail of drugs that include steroids, antivirals, antibiotics and compounds like ammonium glycyrrhizinate which should be viewed with caution as some of these are known to cause hepatic injury. Especially in the setting of hypoxia and cytokine storm, use of these drugs can exacerbate any existing hepatic insult. Special caution is warranted for patients with pre-existing liver disease. At the moment, there is lack of robust data to support the use of specific hepato-protective agents. However, in cases of severe liver injury, liver protective agents have been used in COVID-19. Figure 3 succinctly delineates the diagnostic approach to COVID-19 patients with abnormal liver biochemistries, investigations to be performed and monitoring of such patients.

In the face of this pandemic, management of patients with chronic liver disease has also posed problems. Recently, the AASLD and EASL have come up with recommendations for patients with compensated as well as decompensated liver disease. In case of compensated liver disease, AASLD recommends limiting outpatient visits and to consider seeing in person only new adult and paediatric patients with urgent issues and clinically significant liver disease (*e.g.*, jaundice, elevated ALT or AST > 500 U/L, recent onset of hepatic decompensation), to continue treatment for hepatitis B and hepatitis C if already on treatment, to continue monitoring in those on or off therapy for hepatocellular carcinoma (HCC), to continue surveillance in those at

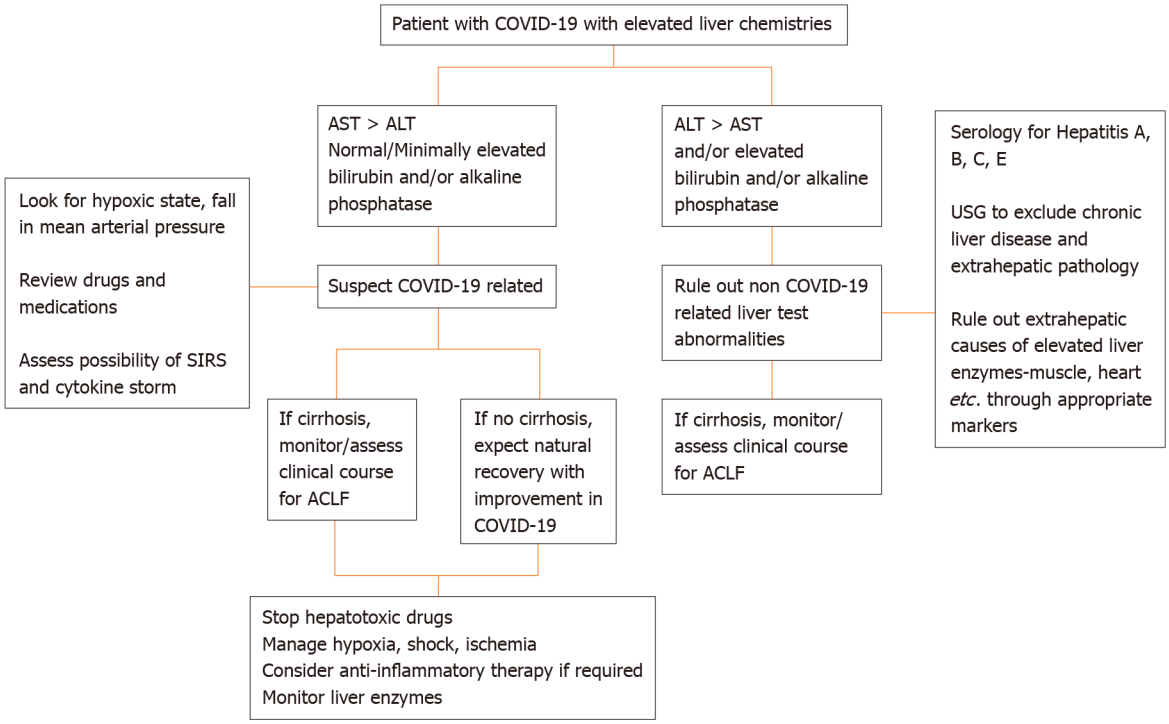

Figure 3 Approach to a coronavirus disease 2019 patient with liver dysfunction. COVID-19: Coronavirus disease 2019; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ACLF: Acute-on-chronic liver failure; USG: Ultrasonography.

risk for HCC and to proceed with HCC treatments when able rather than delaying them due to the pandemic[75]. In those with decompensated liver disease, AASLD recommends evaluating only patients with HCC or those patients with severe disease and high MELD scores who are likely to benefit from immediate liver transplant listing[75]. In autoimmune liver disease too, EASL recommends against reducing immunosuppressive therapy unless indicated in special circumstances[76].

LIVER DYSFUNCTION AND PROGNOSIS

The prognostic variables of hepatic dysfunction in COVID-19 are still being worked out. As previously mentioned, patients with more severe disease have abnormal levels of transaminase levels, suggesting that elevated transaminase levels may be viewed as a prognostic factor and these patients need to be treated with caution. However, the causality association of this factor might be subject to bias. In a retrospective study from Wuhan by Zhou *et al*[77], several factors were identified that might be associated with higher mortality in adults who were hospitalised with COVID-19. Older age, d-dimer levels greater than 1 μg/mL, and higher Sequential Organ Failure Assessment (SOFA) score on admission were associated with higher odds of in-hospital death. Also, levels of interleukin 6 (IL-6), high-sensitivity cardiac troponin I, and lactate dehydrogenase (LDH) were elevated and lymphopenia was more common in severe COVID-19 illness. Preliminary data suggests the reported death rate varies depending on the study and country. However, the mortality rate estimates are based on the number of deaths relative to the number of confirmed cases of infection, which is not representative of the actual death rate. Extrapulmonary involvement like hepatic and renal injury could indicate more severe inflammatory responses and might have a bearing on the mortality rates. Furthermore, it is not clear at this point of time whether the algorithms and scores that are commonly used to assess prognosis in patients with acute hepatic failure are applicable to liver injury in COVID-19, considering the multiple factors involved in the pathogenesis. This, therefore, warrants extreme degree of caution and an individually tailored approach while dealing with such patients.

CONCLUSION

SARS-CoV-2 infection has taken the world by storm. The pandemic is yet to reach a plateau, with the incidence rising and newer populations getting infected. However, physicians, researchers and scientists have left no stone unturned to understand the pathogenesis of this multi-system afflicting disease, find out effective therapies and contain the pandemic. While the disease primarily affects the respiratory system, liver injury does pose problems in the management of COVID-19 patients. Both direct virus-mediated cytopathic effects and indirect immune mediated, drug induced or hypoxic states are probably responsible for causing and perpetuating the liver injury. However, a word of caution: Transaminitis in patients with COVID-19 should not be overly investigated. Only in those patients where there is suspicion of cholestatic pattern of injury, investigations like ultrasonography and magnetic resonance cholangiopancreatography may be performed. Besides, although it may sound slightly premature, in view of the recent case report, clinicians should also, in this era of COVID-19 infection, keep in mind that acute non-icteric hepatitis may be the virus's initial presentation prior to the development of respiratory symptoms[38]. As new evidence trickles in and more facts come to light, we will be in a better position to understand and tackle liver injury in COVID-19. Intensive monitoring and individually tailored approach are the need of the hour to treat patients with severe liver injury or patients with pre-existing liver diseases.

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