COVID-19 and the liver: overview

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On 12 March 2020, the WHO declared that the coronavirus disease 2019 (COVID-19) constitutes a pandemic. Cases of liver damage or dysfunction (mainly characterized by moderately elevated serum aspartate aminotransferase levels) have been reported among patients with COVID-19. However, it is currently uncertain whether the COVID-19 related liver damage/dysfunction is due mainly to the viral infection by itself or other coexisting conditions, such as the use of potentially hepatotoxic medications and the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and multiple organ dysfunction. Individuals at high risk for severe COVID-19 are typical of older age and/or present with comorbid conditions such as diabetes, cardiovascular disease, and hypertension. This is also the same profile for those at increased risk for unrecognized underlying liver disease, especially nonalcoholic fatty liver disease. This could make them more susceptible to liver injury from the virus, medications used in supportive management, or hypoxia. So the aim of this review was to illustrate the clinical implications of COVID-19 on the liver in healthy and diseased states as well as the implications of common liver disorders on the outcome of COVID-19. Eur J Gastroenterol Hepatol 33: 309–311

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen of 2019 novel coronavirus disease (COVID-19), has posed a serious threat to global public health. The WHO has declared the outbreak of SARS-CoV-2 infection an international public health emergency. Lung lesions have been considered as the major damage caused by SARS-CoV-2 infection. However, liver injury has also been reported to occur during the course of the disease in severe cases [1].

One study in China showed that up to half of people with the new coronavirus, named SARS-CoV-2, had liver dysfunction at some point during their illness. It is not clear if the reason lay with the virus or the strong medications used to fight it. Also unclear is if COVID-19 makes existing liver disease worse [2].

Liver injury is associated with COVID-19 infection

Respiratory symptoms are the most common presentation, but they are not the only early signs of COVID-19. Diarrhea, nausea, vomiting, and abdominal pain were well documented and often preceded respiratory symptoms [3].

A recently published study also indicates that COVID-19 was detected in the stool of over 50% of infected hospitalized patients. Investigators found that the lamina propria of the stomach, duodenum, and rectum was edematous with infiltrating plasma cells and lymphocytes [4]. Viral host receptor angiotensin-converting enzyme 2 (ACE2) and viral nucleocapsid protein stained positive in specimens, making gastrointestinal infection with COVID-19 – and fecal-oral transmission – likely. Fecal shedding of viral RNA was also found in 20% of patients with COVID-19, despite real-time reverse transcriptase PCR testing from two sequential respiratory tract specimens collected at least 24 h apart being negative. These results have a clear impact regarding transmission precautions, especially in hospitalized patients [4].

A number of studies have shown that liver injury occurred in patients with SARS, which was mainly manifested in the mild and moderate elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) during the early stage of the disease. Some patients had decreased serum albumin and increased serum bilirubin levels [5,6]. The severe cases were more likely to have severe liver injury compared to mild cases [1,7].

Recent studies on COVID-19 have shown that the incidence of liver injury ranged from 14.8 to 53%, mainly indicated by abnormal ALT/AST levels accompanied by slightly elevated bilirubin levels [8,9]. The albumin is decreased in severe cases and the level of albumin is around 26.3–30.9 g/L [10].

A recent study of nearly 1100 Chinese patients, Guan *et al*. documented that elevated serum AST levels were observed in nearly 18% of patients with non-severe COVID-19 disease and in approximately 56% of patients with severe COVID-19 disease [11]. Moreover, in that study, elevated serum levels of ALT were also observed in nearly 20% of patients with nonsevere COVID-19 disease and in approximately 28% of patients with severe COVID disease [11].

In death cases of COVID-19, the incidence of liver injury might reach as high as 58.06 and 78% [12,13]. One study reported that serum ALT and AST levels increased up to 7590 and 1445 U/L, respectively, in a patient with severe COVID-19 [10].

European Journal of Gastroenterology & Hepatology 2021, 33:309–311

Keywords: coronavirus disease 2019, hepatitis, liver cirrhosis, liver injury, liver transplantation, nonalcoholic fatty liver disease

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Received 26 April 2020 **Accepted** 14 May 2020

Several possible mechanisms of liver injury were proposed, this novel coronavirus may produce, in some cases, relevant hepatic damage, probably through the immune interactions requiring the action of intrahepatic cytotoxic T cells and Kupffer cell [14]. Postmortem biopsies were recently performed in a death COVID-19 patient, and the results showed moderate microvascular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury [15]. Direct cytotoxicity due to active viral replication in hepatic cells: SARS-CoV-2 binds to target cells through ACE2. Because ACE2 is expressed abundantly in the liver and in particular on biliary epithelial cells, the liver is a potential target for direct infection, which was; however, not yet demonstrated [16]. Hypoxia and shock induced by COVID-19-related complications (such as respiratory distress syndrome, systemic inflammatory response syndrome, and multiple organ failure) may also cause hepatic ischemia and hypoxia-reperfusion dysfunction [17]. A recent study reported that the liver injury observed in COVID-19 patients might be caused by lopinavir/ritonavir, which is used as antivirals for the treatment of SARS-CoV-2 infection [9].

Impact of COVID-19 in patients with chronic liver disease and cancer

No evidence suggests that patients with controlled chronic hepatitis B or C virus infection are at increased risk of SARS-CoV-2 infection. However, these patients, often have other comorbidities such as diabetes, hypertension, and cardiovascular disease which increase the risk of serious illness from COVID-19 [18].

Infection with COVID-19 may impact existing chronic liver disease in different ways: the additional hepatic injury induced by the COVID-19 could lead to hepatic decompensation in patients with compromised hepatic reserves, the potential immunosuppressive properties induced by the SARS-CoV-2 may lead to viral reactivation in patients with chronic viral hepatitis which need to be further confirm and in other studies and lastly drugs used for the treatment of COVID-19 or its complications may produce hepatotoxicity [15].

Recent study showed that patients with nonalcoholic fatty liver disease (NAFLD) had a higher risk of progression to severe COVID-19 and longer viral shedding time [19]. Obesity and NAFLD have been associated with increased production of pro-inflammatory cytokines like TNF-α by adipose cells and Kupffer cells. It remains speculative that the impaired innate immunity, manifested by derailed functional diversity of macrophages, imbalance between inflammation-promoting M1 macrophages and inflammation-suppressing M2 macrophages will lead to the progression of COVID-19 [20].

Data on the prevalence and impact of COVID-19 on cancer patients have gradually emerged. According to a prospective nationwide cohort study in China, researchers identified 18 of 1590 (1%) patients with both confirmed COVID-19 and a history of cancer. The cancer cohort experienced more severe disease and was more likely to be admitted to intensive care or die. Cancer therapy within 1 month also increased the risk of severe disease [21].

Table 1. Main characteristics related to liver disease in patients with COVID-19 infections in different regions

Author (year)	Country	Sample size	Abnormal AST(%)	AST (IU/L)	Abnormal ALT(%)	ALT (IU/L)	Male, *n* (%)	Age (years)	Severe disease (%)	No severe disease	History of liver disease %	Antibiotics drugs (%)	Antiviral %	Antifungal %
Guan (2020) [11]	China (Multicenter)	1099	168 (22.2)	NA	158 (21.3)	NA	640 (58.2)	47.0 (35.0–58.0)	173 (15.7)	926 (84.3)	23 (2.1)	632 (57.5)	393 (35.8)	30 (2.7)
Xu (2020) [25]	China (Zhejiang)	62	10 (16.1)	26 (20–32)	NA	22 (14–34)	36 (58.1)	41.0 (32.0–52.0)	NA	NA	7 (11.3)	28 (45.2)	55 (88.7)	NA
Chen (2020) [10]	China (Wuhan)	99	35 (35.3)	34 (26–48)	28 (28.2)	39 (22–53)	67 (68.7)	55.56 35.1	NA	NA	11 (11.1)	70 (70.7)	75 (75.8)	15 (15.2)
Chen (2020) [26]	China (Wuhan)	29	7 (24.1)	NA	5 (17.2)	NA	21 (72.4)	56.01[a]	14 (48.3)	15 (51.7)	NA	NA	NA	NA
Wang (2020) [3]	China (Wuhan)	138	NA	31 (24–51)	NA	24 (16–40)	75 (54.3)	56.0 (42.0–68.0)	36 (26.1)	102 (73.9)	4 (2.9)	89 (64.5)	124 (89.9)	NA
Pan (2020) [27]	China (Wuhan)	21	NA	32±20 (15–95)	NA	42±31 (12–107)	6 (28.6)	40.06 9.0	0 (0.0)	21 (100.0)	NA	NA	NA	NA
Liu (2020) [28]	China (Multicenter)	32	2 (6.2)	25 (19–32)	9 (28.1)	26 (17–46)	20 (62.5)	38.5 (26.3–45.8)	4 (12.5)	28 (87.5)	1 (3.13)	NA	NA	NA
Huang (2020) [8]	China (Wuhan)	41	15 (36.6)	34 (26–48)	NA	32 (21–50)	30 (73.2)	49.0 (41.0–58.0)	13 (31.7)	28 (68.3)	1 (2.4)	41 (100.0%)	38 (92.7%)	NA
Chen (2020) [29]	China (Wuhan)	9	3 (33.3)	24 (21–119)	3 (33.3)	16 (11–58)	0 (0)	28 (26–34)	0 (0.0)	9 (100.0)	NA	9 (100.0%)	6 (66.7%)	NA
Qingxian (2020) [30]	China (Shenzhen)	417	150 (35.9)	38 (28–52)	187 (44.84)	46 (27–76)	198 (45.32)	47 (34–60)	85 (20.38)	233 (55.88)	21 (5.04)	47 (52.22)	288 (90.57)	NA

Liver diseases: any liver disease that can cause liver enzyme changes, such as viral hepatitis, autoimmune hepatitis, etc. Normal range for AST and ALT: AST < 40 IU/L and ALT < 40 IU/L.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; NA, not available.
[a]Median, no interquartile range.

In a different retrospective cohort of 28 cancer patients admitted for COVID-19 infection across three hospitals in Wuhan, China, receipt of cancer therapy within 14 days was associated with a substantially higher risk of mortality [22]. Collectively, these studies raise the possibility that patients with cancer may be more susceptible to severe COVID-19 infection than the general population [21,22].

Data on COVID-19 in liver transplant patients are scarce. Whether liver transplant recipients are more susceptible to SARS-CoV-2 infection is a matter of concern, but so far there have been no specific recommendations from major societies. A case series from Italy showed that children who had received liver transplants, despite being immunosuppressed, were not at increased risk of severe pulmonary disease compared with the general population [23].

Post-transplant metabolic complications (e.g. arterial hypertension, chronic renal insufficiency, diabetes, hyperlipidemia, and weight gain) might outweigh immunosuppression as a risk factor for the development of severe COVID-19 disease in patients who have received liver transplants, in line with data from China, which suggest that comorbidities are associated with a worse prognosis [11].

In keeping with clinical insights from the American Association for the Study of Liver Diseases, immunosuppression should not be reduced or stopped in asymptomatic liver transplant recipients [24].

Summary of the published data on COVID-19 illustrating the effects on the liver is shown in Table 1.

In conclusion, individuals with severe forms of COVID-19 tend to develop important alterations of liver enzymes and to have changes of coagulative and fibrinolytic pathway profile, due to the innate immune response against the virus. Further studies are needed to better investigate the causes of liver injury in patients with COVID-19 and the effect of treatment for COVID-19 on the liver.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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