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WORD COUNT	4545	TIME SUBMITTED	09-NOV-2022 10:32PM
		PAPER ID	92463604

COVID-19 and liver: Are footprints still there?

Gupta T *et al*. COVID-19 and liver

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Abstract

The coronavirus disease 2019 (COVID-19) hit the entire world as a global pandemic and soon became the most important concern for all patients with chronic diseases. Early trend in higher mortality in patients with acute respiratory distress attracted all researchers to closely monitor patients for other system involvement. Soon it became apparent that patients with chronic liver diseases are at increased risk of mortality given their cirrhosis associated immune dysfunction. Additionally, liver function abnormalities were noticed in patients with severe COVID-19 disease. Profound cytokine storm, direct viral infection, drugs and reactivation of viral infections were causes of deranged liver functions. Here, we discuss the relation between COVID-19 and chronic liver disease, specifically cirrhosis, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease (NAFLD), as well as the liver manifestations of COVID-19. The metabolic syndrome, obesity, diabetes mellitus and NAFLD were found to worsen outcome in different studies reported all over the globe. Decompensated cirrhosis should be considered as a risk factor for death and severe COVID-19 disease. Recently, COVID-19 related cholangiopathy has also been reported with changes of secondary sclerosing cholangitis. The concern about long term persistence of viral antigens in gut epithelia raises the concern for future risk of autoimmune liver diseases.

Key Words: COVID-19; Chronic liver disease; Cirrhosis; Liver injury; Transaminases; Non-alcoholic fatty liver disease; Post-acute COVID-19 syndrome

Gupta T, Sharma H. COVID-19 and liver: Are footprints still there? *World J Gastroenterol* 2022; In press

Core Tip: Coronavirus disease 2019 (COVID-19) and liver involvement had been a major concern since beginning of COVID-19 pandemic. Deranged liver functions with raised transaminases were reported in patients with severe COVID-19 disease. On the other hand, acute hepatitis or liver failure was uncommon. Severe acute respiratory syndrome coronavirus 2 virus associated cytokine surge, systemic inflammation, direct viral infection, drugs like remedisivir, steroids, lopinavir-ritonavir were main causative factor for raised transaminases. Patients with pre-existing chronic liver diseases especially non-alcoholic fatty liver disease were found to be risk factor for causing increased mortality in patients with severe COVID-19 disease.

INTRODUCTION

In December 2019, severe acute respiratory illness (SARS) as caused by the SARS-coronavirus 2 (SARS-CoV2) virus (Coronaviridae family) was first detected in Wuhan, China. It soon spread to the rest of the world, being declared as a global pandemic in March 2020. In mild cases, the symptoms included fever, coughing, body aches, malaise, loss of taste and smell. Approximately 15% of patients would eventually have respiratory compromise, hypoxia, and the need for invasive mechanical ventilation. Finally, multi-organ failure, coagulopathy, disseminated intravascular coagulation, acute respiratory distress syndrome, and hypoxia would follow. Over a period of more than 2 years, multiple waves of coronavirus disease 2019 (COVID-19) were observed in different geographical regions. As the virus mutated, there were many shifts in the clinical presentation. The new symptoms of predominant upper respiratory tract like sneezing, rhinitis, gastrointestinal symptoms like diarrhea, non-specific abdominal pain, cardiac symptoms with arrhythmias, ocular and neurological symptoms were reported. Additionally, as patients underwent more investigations, dysregulated coagulation and thrombosis were documented. Overall, liver involvement as elevated liver enzymes ranging from 14% to 53% of patients in various studies was documented. However, acute hepatitis or liver failure was uncommon. Furthermore, different studies worldwide

have shown that non-alcoholic fatty liver disease, diabetes, hypertension, and obesity are significant risk factors for severe COVID-19 illness.

A lockdown and a ban on air travel during the COVID-19 epidemic helped keep people with chronic illnesses at home. Their overall exposure to COVID-19 and other pathogens was constrained. Mild COVID-19 disease patients were isolated and quarantined in accordance with protocol and did not frequently undergo examinations. Patients with serious illnesses, however, were the only ones who underwent in-depth examinations. As a result, the majority of research mainly included individuals with serious diseases.

METHOD

We searched PubMed, Google Scholar, and Google from January 2020 to Aug 2022, for articles written in English that describe the liver effects of COVID-19, using the search terms "coronaviruses and liver", "COVID-19 and liver", "COVID-19 and liver symptoms", "COVID-19 and hepatic", "COVID-19 and liver function test", "COVID-19 and liver inflammation", "SARS-Cov-2 and liver", "COVID-19 and NAFLD", "COVID-19 and non-alcoholic fatty liver disease", "COVID-19 and non-alcoholic fatty liver disease", "COVID-19 and hepatitis", and "COVID-19 and Vaccine". Reference lists of the articles were scanned to identify any additional studies. The articles' title and abstract were read for the initial selection and then the full-text articles were found out and read on availability. Reference lists of the full-text articles were scanned to identify any additional studies. All types of research articles, including original research articles, reviews, case series, short communications, and case reports were considered. Of the 667 articles identified, 313 were studied for preparing the review article.

SARS-COV2 HEPATOTROPISM

Due to a lack of significant laboratory testing and tissue biopsies from patients who were actively infected with SARS-CoV2, the mechanism of its replication is still not entirely understood.

SARS-Cov2 is an enveloped positive sense single stranded RNA virus having almost 80% identity with SARS-CoV virus. It has 4 structural proteins namely nucleocapsid, spike (S), membrane and enveloped proteins. The spike protein has multiple protrusions from the cell surface giving the virus its appearance and name. The ACE2 receptors are the potential site of entry for SARS-Cov2 virus. ACE2 receptors are present abundantly on alveolar epithelium, lung, nasal epithelium *etc.* They are also present in less numbers in intestinal epithelium and liver[1]. The spike protein having two subunits S1 and S2 interacts with ACE2 receptor for virus entry. However, ACE2 receptors are not sufficient alone and transmembrane serine proteases 2 (TMPRSS2) in addition to basic amino acid cleaving enzymes (FURIN) are essential for virus entry. According to single cell RNA sequencing analysis, hepatocytes have less co-expression of TMPRSS2 and ACE2 receptors. In the liver, cholangiocytes and sinusoidal endothelial cells have the highest expression of the ACE2 gene in almost 60% of the cell population as compared to hepatocytes (3% cells)[2,3]. So, a tissue or organoid model is required to understand the permissibility of liver cell types to SARS CoV-2 infection. Zhao *et al*[4] created human liver ductal organoids that were able to replicate the SARS-CoV2 infection and expressed ACE2 and TMPRSS2. This suggests that the bile duct epithelium may be able to support pseudoparticle invasion. Despite a higher number of SARS-CoV2 virus receptors and a higher risk of infection of bile duct epithelia, the COVID-19 disease does not follow a cholestatic pattern[5].

Studies conducted before the COVID-19 pandemic indicated that patients with hepatitis C virus (HCV)-related cirrhosis had 30 times higher ACE2 receptor expression on their hepatocytes than healthy individuals[6]. The overexpression of ACE2 and TMPRSS2 has also been documented in obesity and nonalcoholic steatohepatitis patients, but not in patients with steatosis alone[7]. ACE2 is an interferon-inducible gene found in human respiratory epithelia, possibly SARS-CoV2 hepatotropism can be potentiated by effects of systemic inflammation on hepatocytes and can lead to hepatocyte injury[8,9].

Additionally, ACE2 receptors are found in intestinal epithelia/ enterocytes and SARS-CoV2 RNA has been documented by polymerase chain reaction in stool up to

one week after recovery from respiratory illness. Latest data suggests that viral protein and RNA are found in intestinal biopsies for several months after resolution of respiratory illness[5,10].

In a study from Italy, postmortem wedged liver biopsy samples of 48 patients dying from severe COVID-19 disease were examined[11]. It revealed vascular abnormalities like sinusoidal and partial to complete portal venous microthromboses in almost 100% of samples. Additionally, mild portal inflammation, portal fibrosis, microvesicular and macrovesicular steatosis could be documented in 66%, 60%, and 50% of patients respectively. The latter finding is probably related to pre-existing liver disease like nonalcoholic fatty liver disease (NAFLD), as suggested by presence of metabolic risk factors which were more prevalent in this patient group. The electron microscopy of these biopsies also revealed potential coronavirus-like particles, mitochondrial edema, and apoptosis of hepatocytes. However, comprehensive proteomic analysis of autopsy tissue from 19 patients with COVID-19 did not find signs of viral replication[12].

Further, proteomic profiling revealed disrupted oxidative phosphorylation, fatty acid oxidation, and up-regulated immunological activators and profibrotic pathways. Possibly, hepatic steatosis, coagulative necrosis, and multiorgan dysfunction were all linked to mitochondrial dysfunction, dysregulated oxidative phosphorylation, *etc*[13].

LIVER FUNCTION TEST AND COVID-19

Despite higher SARS-CoV2 receptor expression on cholangiocytes and SECs, the liver function derangement is usually in the form of mild elevation of liver enzymes [1-2 upper limit of normal (ULN)][14-16].

Singh *et al*[17] showed that the presence of pre-existing liver illness has no effect on the incidence of liver enzyme elevations, although patients with pre-existing liver disease had a higher mortality rate.

In COVID-19 disease SARS-CoV2 induces systemic inflammatory response and release of cytokines. The most implicated molecules are interleukin-6, tumor necrosis factor alpha (TNF-alpha). Elevated cytokines result in hepatocyte inflammation and

injury with liver ischemia, hypoxia, worsening of already existing chronic liver disease (CLD) and/or toxicity of medications used to treat the illness (Figure 1). Hepatic congestion as well as potential direct infection of hepatocytes though uncommon may also result in release of transaminases[18].

However, indicators of muscle breakdown or systemic inflammation did not correlate with serum aspartate amino transferase (AST) and alanine amino transferase (ALT) levels in hospitalised COVID-19 patients[19,20].

Because AST was frequently observed to surpass ALT throughout the course of COVID-19, this was similar to patients with alcoholic liver disease, ischemic hepatitis and cirrhosis compared to a traditional hepatocellular pattern where ALT is more than AST[19]. Possibly, COVID-19 related mitochondrial dysfunction results in hepatic steatosis and altered hepatic perfusion is the result of sinusoidal microthrombosis[11,21-23].

The respiratory epithelia involvement by SARS-CoV2 virus leads to defective oxygenation and release of cytokines causes peripheral vasodilation and reduced tissue perfusion; the resultant perfusion and oxygenation defect causes systemic hypoxia which is a contributory factor in hepatocyte injury[24].

Early on in the pandemic as no definitive treatment was available, experimental therapies in the form of drugs such as tocilizumab, remdesivir and lopinavir-ritonavir were used, which are known to cause hepatic injury[25-29]. Remedisivir was documented to cause elevations in liver enzymes in different studies[30,31]. Tocilizumab was well known for its risk of hepatitis B virus (HBV) reactivation and screening of hepatitis B and hepatitis C was advised before its use.

Ponziani *et al*[32] and Yip *et al*[33] showed that elevation of liver enzymes were associated with increased incidence of shock, ICU admissions and Invasive ventilation. But these studies could be biased as hospitalized patients with severe disease undergo intensive liver function test monitoring (which increases the chances of detecting liver injury) as compared to home isolated patients with mild disease due to quarantine.

Some studies have suggested that there is no apparent correlation between liver function derangement and mortality[34,35]. While others have suggested an increased risk of death in patient with ALT levels > ULN[16,36,37].

According to Bangash *et al*[38], elevated liver transaminases linked to COVID-19 infection are more likely caused by the severity of the illness, in which the host's reaction and iatrogenic factors like medication and invasive ventilation cause bystander liver injury and thus explain its link to mortality in a manner similar to that of sepsis[38]. Because of this, clinicians must focus more on these factors than just elevated aminotransferases especially in patients with no pre-existing liver disease.

COVID-19 AND CLD

In early days of COVID-19 pandemic, hepatology community worked fast to establish the risk of SARS-CoV2 acquisition and harmful COVID-19 outcome in pre-existing CLD. According to data from major case series and population-level electronic health records during the first global spike, patients with CLD were not overrepresented, indicating that these diseases did not make patients more susceptible to infection[15,39]. In fact, a significant North American study discovered that people with cirrhosis had a decreased probability of SARS-CoV2 positivity, probably due to improved awareness, testing, and patient adherence to public health recommendations for home isolation and quarantine. However, it is now evident that individuals with cirrhosis are more likely to experience negative COVID-19 outcomes after infection, including mortality. Multiple lines of evidence, such as findings from international registries SECURE-Cirrhosis and COVID-Hep[40], sizable observational cohorts like COVID-Cirrhosis-CHESS group[41], and population-level data, have all been used to support this. These registries were made early in the pandemic and interestingly, with emergence of new delta and omicron variants as well as introduction of vaccines, the relation between COVID-19 and liver shall continue to evolve.

In a large registry cohort of 729 patients from 29 countries, it was discovered that mortality in individuals with cirrhosis after SARS-CoV2 infection was 32 percent overall, with case fatality increasing gradually with each Child-Pugh (CP) class

(CLD without cirrhosis: 8 percent, CP-A: 19 percent, CP-B: 35 percent, CP-C: 51 percent)[42]. The rates of invasive mechanical ventilation, renal replacement treatment, and intensive care unit (ICU) hospitalisation all showed similar stepwise trajectories. Additionally, after adjusting for age and comorbidities, patients with decompensated cirrhosis (CP-B and CP-C) had a considerably higher probability of dying than contemporaneous patients without cirrhosis who tested positive for SARS-CoV2. Additionally, reports of elevated COVID-19 mortality in cirrhosis have been confirmed in two Asian-only registries[43] and in numerous multicenter cohort studies conducted in various geographic locations[44-46]. Iavarone *et al*[44] observed a 30-d mortality of 30% in Northern Italy during the early stages of the pandemic, which was much greater than a historical cohort of patients with cirrhosis hospitalised with bacterial infection[44]. Decompensated cirrhosis was also reported as an independent risk factor of death in CLD patients across 21 North American institutions[45]. Additionally, individuals with hepatocellular carcinoma (HCC) had a sevenfold higher chance of dying from COVID-19 than patients of cirrhosis without HCC, indicating that this population may be particularly vulnerable to the side effects of SARS-CoV2 infection. A retrospective French cohort of > 259000 COVID-19 inpatients, including > 15000 with pre-existing CLD showed, that patients with decompensated cirrhosis had a higher adjusted risk for COVID-19 mortality[47]. This was in contrary to nationwide Swedish cohort's findings, which failed to identify a connection between cirrhosis and COVID-19 related mortality[48]. Cirrhosis overall, and decompensated cirrhosis in particular, should be considered a risk factor for death and severe COVID-19.

There are various characteristics of the COVID-19 clinical course in cirrhotic individuals. First, up to 46% of patients can present with acute hepatic decompensation, usually with new or worsening ascites and/or hepatic encephalopathy (HE)[42]. This can happen between 20% and 58% of the time even in the absence of the usual COVID-19 respiratory symptoms[42,44]. Patients with CLD present with gastrointestinal (GI) symptoms more frequently than matched controls[42] and it is linked to a more severe disease trajectory[45], a phenomenon that is widespread in society[49] and is connected to increased intestinal permeability,

electrolyte imbalance, and systemic inflammatory load, being documented in up to 12% to 50%[42-44,46] of patients with COVID-19 and decompensated cirrhosis. In the context of COVID-19, a number of well-known prognostic scoring models have been used to assess cirrhosis, with the CLIF-C ACLF score and CLIF organ failure scores surpassing MELD, NACSELD, and CP scores in the international and Latin American cohorts, respectively[42,50]. In actuality, the likelihood of recovery rapidly decreases as organ support requirements increase. For instance, patients with CP-C cirrhosis have a mere 21% probability of surviving if admitted to the ICU, and that chance drops to 10% if mechanical breathing is used[42].

Despite the fact that SARS-CoV2 infection causes immediate hepatic decompensation, respiratory failure (71%) and problems related to the liver (19%) are the primary causes of death in individuals with cirrhosis[42]. Hepatic dysfunction and lung damage are likely linked by a number of overlapping pathways (Figure 2), including immunological dysfunction brought on by cirrhosis, coagulopathy, and altered pulmonary dynamics brought on by ascites and HE[51]. Given that the composition of the gut microbiota has been demonstrated to influence how the host immune system reacts to COVID-19, it is conceivable that intestinal permeability and dysbiosis linked to cirrhosis may also have a negative effect[52,53].

Although COVID-19 in patients with cirrhosis is linked to a significant immediate risk of death, rates of mortality and re-admission at 90 days appear equivalent to those with cirrhosis alone in those who survive the initial shock[54]. Therefore, it appears that SARS-CoV2 infection does not accelerate the progression of liver disease beyond the course of cirrhosis after the acute infective period. However, up to 4 mo after recovering from acute COVID-19, hepatic MRI alterations, including as enhanced T1 signaling, raised fat fraction, and hepatomegaly, have been found in 10% to 28% of otherwise healthy people[55,56]. In both patients with and without underlying CLD, it is yet unknown what these radiological characteristics following COVID-19 mean clinically in the long run. Furthermore, although this remains unexplored and is not considered in the current investigations, these hepatic abnormalities might not be exclusive to COVID-19 and might also be present in individuals recovering from other severe systemic insults.

It is crucial to note that studies undertaken in the years before COVID-19 vaccination and the appearance of viral variants like Delta and Omicron are largely responsible for our knowledge of the disease course in individuals with COVID-19 and cirrhosis. CLD can affect 1% to 11% of people with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection[57]. Numerous liver cirrhosis patients have been shown to have drunk alcohol in an ineffective effort to ward off coronavirus infection, raising the risk of alcoholic hepatitis[58].

Implications of COVID-19 include increased mortality associated with severe COVID-19 infections, increased risk of hepatic decompensation, and decreased routine various and HCC surveillance.

Although the acute mortality associated with COVID-19 in patients with cirrhosis is substantial, the rates of death and readmission at 90 d are equivalent to those in patients with cirrhosis alone in those who survived the initial insult[54]. Therefore, SARS-CoV2 infection does not appear to accelerate the course of liver disease beyond the typical history of cirrhosis after the acute infective period.

It is well known that infections put people at risk for decompensation (worsening ascites, encephalopathy, or acute kidney injury), and in the case of COVID-19, which is characterized by significant cytokine activation, cytokine-induced hepatocyte apoptosis and necrosis in the presence of decreased liver reserve may result in hepatic decompensation. To rule out COVID-19 as a possible cause, patients with cirrhosis who exhibit decompensation should be evaluated.

CLINICAL OUTCOMES OF PATIENTS WITH INDIVIDUAL UNDERLYING LIVER DISEASES

COVID-19 and Chronic HBV and HCV infection

As there are many etiologies (part of a systemic illness, immune mediated, direct SARS-CoV-2 infection, viral hepatitis, drug induced, and ischemic hepatic injury) which can cause derangement of LFTs, one of which is chronic HBV and HCV infection, it is always important to look for an underlying chronic hepatitis B or hepatitis C infection[59,60].

Prednisolone and tocilizumab were used in the treatment of COVID-19, which is known to enhance the likelihood of HBV reactivation and flare-up alongside HCV flare-up. When starting COVID-19-related therapy in people with advanced liver disease brought on by HBV and HCV, care must be taken[59,60]. Although the risk/benefit of an intervention is likely to weigh strongly when dealing with the very deadly disease of COVID-19, established criteria in such cases need to be followed to limit the risk for hepatic decompensation (Table 1).

COVID-19 and NAFLD

The general population's risk factors for COVID-19 morbidity and mortality include advancing age, obesity, and diabetes[6].· Regarding how NAFLD affects the COVID-19 course, there are significant differences found throughout the studies. This gap may be attributable to problems in distinguishing the impact of NAFLD from other metabolic comorbidities due to the confounding effect of virally induced steatosis or because of different diagnostic criteria. This last point is especially crucial right now as the hepatology community at large struggles with the proposed classification modifications from NAFLD to metabolic dysfunction-associated liver disease[39]. Studies have shown obesity to be associated with increased severity and mortality in COVID-19. On the other hand, patients of obesity have higher prevalence of diabetes, NAFLD, dyslipidemia, hypertension and metabolic syndrome. In a retrospective series of 202 patients with SARS-CoV2 infections, NAFLD has been identified as a risk factor for progressive COVID-19, abnormal liver enzyme levels, and extended viral shedding times[61]. A study with 327 participants revealed connection between NAFLD and the likelihood of severe COVID-19 in people under 60 years age[62]. Similar to this, MRI results from 287 SARS-CoV2 patients (79 positive, 208 negative) showed that people with obesity and a concurrent liver fat fraction of less than 10% were three times more likely to develop symptoms of laboratory-confirmed COVID-19 (available as a non- peer-reviewed Preprint only)[63].

The chronic low-grade inflammation in NAFLD shifts the macrophages from M2 to M1 phenotype causes activation of hepatic stellate cells and innate immune

system which in collaboration with profound systemic inflammation in COVID-19 disease leads to hepatocyte injury, necrosis, and apoptosis (Figure 3).

Targher *et al*[64] reported high FIB-4 and NFS score with increased COVID-19 disease severity. Similarly, Lopez-Mendez *et al*[65] showed steatosis and fibrosis to be linked with increased chances of ICU admissions. However, due to constraints of isolation, quarantine and adequate manpower, there was lack of detailed history, tissue histology, therefore, we do not have comparative studies of liver steatosis, steatohepatitis and fibrosis with relation to COVID-19 disease severity. COVID-19 pandemic severely affected Hepatology services in early diagnosis, surveillance programs, implementation of hepatitis B and C eradication programs, *etc* (Table 2).

COVID-19 and autoimmune hepatitis

Very little is known regarding the results of COVID-19 in individuals with autoimmune hepatitis (AIH), a rare form of CLD. Marjot *et al*[66] study in October 2020, included more than 1700 participants, aimed to describe the COVID-19 illness course and risk of unfavorable outcomes in 70 individuals with AIH. They showed that, despite the potential reporting of individuals with more severe liver disease, AIH does not significantly increase susceptibility to negative outcomes following SARS-CoV2 infection through several comparisons with non-AIH CLD and non-CLD cohorts. In contrast to the use of immunosuppressive, for which no adverse effects were found, age and the severity of baseline liver disease continue to be the most significant drivers of outcome in this patient group[45]. This should reassure patients and medical professionals and support suggestions that immunosuppressive medications shouldn't be frequently changed or stopped during COVID-19.

COVID-19 cholangiopathy

There are few case reports for secondary sclerosing cholangitis in patients with severe COVID-19 disease with histologic changes of cholangiocyte injury and cholangiopathy. These patients had a protracted course and significant liver related

morbidity. Essentially this condition was noticed after recovery of COVID-19 disease, therefore, it was called as Post COVID-19 cholangiopathy[67].

COVID-19 VIRAL ANTIGEN PERSISTENCE IN GUT

Recently, long term sequelae of COVID-19 have been identified with symptoms of fatigue, insomnia, bodyache and cognitive dysfunction. Persistence of viral antigens in gut epithelia have been documented[68]. Possibly these persistent antigens cause immune dysfunction and low-grade persistent inflammation which manifests in various ways. It could be a basis for immune perturbation in post COVID-19. Its effect on liver in post COVID era shall be an area for research.

ADVERSE EFFECT OF mRNA VACCINES

Effects of mRNA vaccines for COVID-19 have been implicated in causation of "immune mediated hepatitis" by production of antibodies against spike protein of SARS-CoV2 virus[69]. It shall be interesting in near future to look for autoimmune hepatitis or immune mediated hepatitis prevalence in community.

CONCLUSION

During COVID-19 infection, liver enzymes may be mildly elevated and generally recover without treatment. Presence of NAFLD has been linked with increase COVID-19 disease severity and ICU admissions. Different studies have shown variable impact of NAFLD on COVID-19 related mortality. In patients with CHB and CHC, mild COVID-19 disease course is well tolerated, whereas in moderate-severe COVID-19 disease requiring steroids and/or tocilizumab, risk of viral flare and worsening of liver disease is present. Patients with compensated cirrhosis are at increased risk of decompensation after COVID-19 illness. In decompensated cirrhosis, the trajectory of COVID-19 disease severity and mortality rises with worsening Child scores. With emerging evidence of persistent gut viral antigens capable of stimulating immune system, we should be vigilant for entity of postacute COVID-19 syndrome.

Figure 1 Effects of COVID-19 and liver injury interaction.

Figure 2 Course of liver cirrhosis during COVID-19. HE: Hepatic encephalopathy.

Figure 3 Complex interplay of non-alcoholic fatty liver disease and COVID-19. COVID-19: Coronavirus disease 2019; NAFLD: Non-alcoholic fatty liver disease; ARDS: Acute respiratory distress syndrome; IL-6: Interleukin-6.

Table 1 Studies showing effect of various etiologies of liver disease on COVID-19

Ref.	Country	Study design	Study population	Sample size	Outcome
HBV					
Anugwom *et al*[70], 2021	China	Letter	Peer reviewed articles with confirmed COVID-19 with HBV information	2054; HBV (*n* = 28)	Inverse relation of HBV with COVID-19
Kang *et al*[71], 2021	Korea	Retrospective, nationwide case-control study	Korean National Health Insurance Service COVID database	7723; HBV (*n* = 267)	Underlying CHB with COVID-19 severity aOR 0.65; 95%CI, 0.57-0.74)
HCV					
Richardson *et al*[15], 2020	United States	Case series	With confirmed COVID-19 and information	5700	HCV infections in < 0.1% (*n* = 3) of COVID-19 patients

			on HCV infection		
Ronderos *et al*[72], 2021	United States	Retrospective single-center	With confirmed COVID-19 and information on HCV infection	1193; HCV (*n* = 50)	HCV infection predictor of in-hospital mortality
NAFLD					
Ji *et al*[62], 2020	China	Retrospective	With confirmed COVID-19 and information on NAFLD status	202; NAFLD (*n* = 76)	HSI with disease progression (OR 6.4; 95%CI 1.5-31.2)
Targher *et al*[64], 2020	China	Prospective observational	Laboratory confirmed COVID-19	310; NAFLD (*n* = 94)	FIB-4 (adjusted OR 1.90, 95%CI 1.33 to 2.72) or NFS (adjusted OR 2.57, 95%CI 1.73 to 3.82) with COVID-19 severity
Lopez-Mendez *et al*[65], 2021	Mexico	Retrospective	Medical records of hospitalized COVID-19	155; liver fibrosis (*n* = 69)	FIB-4 with risk of ICU admission (OR 1.74, 95%CI 1.74-2.68; *P* = 0.023); mortality (OR 6.45, 95%CI

					2.01-20.83, *P* = 0.002)
Sachdeva *et al*[73], 2020	India	Systemic review	-	8142; NAFLD (*n* = 833)	Pooled adjusted 2.358 (95%CI 1.902-2.923) with severity of COVID-19
Mahamid *et al*[74], 2021	Israel	Retrospective case-control	Medical records of COVID-19	71; NAFLD (*n* = 22)	OR 3.57 (95%CI 1.22-14.48) with severity of disease
Hashemi *et al*[75], 2020	United States	Multicentre retrospective	Laboratory confirmed COVID-19	363; NAFLD (*n* = 55)	aOR 2.30, 95%CI 1.27-4.17] with ICU admission
Yao *et al*[76], 2021	China	Retrospective	Laboratory confirmed COVID-19	86; NAFLD (*n* = 38)	OR 11.057 (95%CI 1.193-102.439, *P* = 0.034) with severe illness in COVID-19
Li *et al*[77], 2022	China and United States	Observational; 2-sample mendelian randomization	Laboratory confirmed COVID-19	8267; NAFLD (*n* = 136)	OR 0.97; 95%CI 0.88-1.08; *P* = 0.61 with COVID-19
BCS					
Espinoza *et al*[78], 2021	Brazil	Case report	Laboratory confirmed COVID-19	-	Thrombosis of an abdominal vessel should be considered as a differential diagnosis in patients with undefined

				abdominal pain and elevated liver biochemical tests
Sh Hassan *et al*[79], 2021	Saudi Arabia	Case report	Laboratory - confirmed COVID-19	Thromboembolic events could be the first manifestation of COVID-19

COVID-19: Coronavirus disease 2019; NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 2 Impact of COVID-19 pandemic on hepatology services

Decrease	Increase
OPD follow up and care	Inhospital admission
HBV treatment	Alcohol intake
HCV community level programs	HCC incidence
HCC surveillance and screening	Acute on chronic liver failure
UGI endoscopy	Gastrointestinal bleeding especially variceal bleed
Liver transplantation	Unhealthy lifestyle
	NAFLD/MAFLD

COVID-19: Coronavirus disease 2019; HCC: Hepatocellular carcinoma; UGI: Upper gastrointestinal; NAFLD: Non-alcoholic fatty liver disease; MAFLD: Metabolic associated fatty liver disease.

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ORIGINALITY REPORT

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PRIMARY SOURCES

1	Jean-François Dufour, Thomas Marjot, Chiara Becchetti, Herbert Tilg. "COVID-19 and liver disease", Gut, 2022 Crossref	314 words — 6%
2	www.ncbi.nlm.nih.gov Internet	155 words — 3%
3	www.ajtmh.org Internet	127 words — 3%
4	doi.org Internet	115 words — 2%
5	www.wjgnet.com Internet	49 words — 1%
6	Tobias Boettler, Thomas Marjot, Philip N. Newsome, Mario U. Mondelli et al. "Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic", JHEP Reports, 2020 Crossref	36 words — 1%
7	easl.eu Internet	35 words — 1%
8	eventscribe.com Internet	33 words — 1%

9 Tatyana Kushner, John Cafardi. "Chronic Liver Disease and COVID‐19: Alcohol Use Disorder/Alcohol‐Associated Liver Disease, Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Autoimmune Liver Disease, and Compensated Cirrhosis", Clinical Liver Disease, 2020
Crossref
32 words — 1%

10 Ivana Mikolasevic, Dorotea Bozic, Tajana Pavić, Alen Ruzic et al. "Liver disease in the era of COVID-19: Is the worst yet to come?", World Journal of Gastroenterology, 2021
Crossref
21 words — < 1%

11 Giovanni Targher, Alessandro Mantovani, Christopher D Byrne, Xiao-Bo Wang et al. "Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores", Gut, 2020
Crossref
20 words — < 1%

12 ia801801.us.archive.org
Internet
20 words — < 1%

13 Javier Alejandro Lecca Espinoza, Jorge Elias Júnior, Carlos Henrique Miranda. "Atypical COVID–19 presentation with Budd-Chiari syndrome leading to an outbreak in the emergency department", The American Journal of Emergency Medicine, 2021
Crossref
17 words — < 1%

14 pesquisa.bvsalud.org
Internet
14 words — < 1%

15 Alejandro Campos-Murguía, Berenice M Román-Calleja, José A González-Regueiro, Ivonne Hurtado-Díaz-de-León et al. "Clinical perspectives, assessment,
13 words — < 1%

and mechanisms of metabolic-associated fatty liver disease in patients with COVID-19", World Journal of Gastroenterology, 2021
Crossref

16	staging19.surgery.ucsf.edu Internet	12 words — < 1%
17	www.biorxiv.org Internet	11 words — < 1%
18	www.science.gov Internet	11 words — < 1%
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21	Xinyu Hu, Longyan Sun, Zhaoyang Guo, Chao Wu, Xin Yu, Jie Li. "Management of COVID-19 patients with chronic liver diseases and liver transplants", Annals of Hepatology, 2022 Crossref	9 words — < 1%
22	ml-eu.globenewswire.com Internet	9 words — < 1%
23	onlinelibrary.wiley.com Internet	9 words — < 1%
24	Giovanni Sansoè, Manuela Aragno, Florence Wong. "Covid ‐ 19 and liver cirrhosis: focus on the non ‐ classical renin ‐ angiotensin system and implications for therapy", Hepatology, 2021 Crossref	8 words — < 1%

25	covid19-data.nist.gov Internet	8 words — < 1%
26	egetipdergisi.com.tr Internet	8 words — < 1%
27	www.e-cmh.org Internet	8 words — < 1%
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