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Insight into COVID-19 associated liver injury: Mechanisms, evaluation, and clinical implications

Running Head:

COVID-19 associated liver injury.

Nosheen Nasir[1], 0000-0003-1610-8748

Iffat Khanum[1], 0000-0002-4982-2799

Kiren Habib[1], 0000-0002-9543-6231

Abdullah Wagley [2], 0000-0003-4587-9971

Aleena Arshad[1], 0000-0003-1010-2046

Atif Majeed[3], 0000-0003-2706-1463

[1]Department of Adult Infectious Diseases, Faculty of Medicine, Aga Khan University, Karachi, Pakistan

[2] Research Facilitation Office, Medical College, Aga Khan University, Karachi, Pakistan

[3] Department of Gastroenterology, Faculty of Medicine, Aga Khan University, Karachi, Pakistan

Corresponding author:

Nosheen Nasir FRCP (Edin), FCPS (IM), FCPS (ID), MSc

Assistant Professor, Section of Adult Infectious Diseases

Dept. of Medicine

Aga Khan University, Stadium Road, Karachi 74800, Pakistan

Email: Nosheen.nasir@aku.edu

Phone no: +922 3332133936

https://orcid.org/0000-0003-1610-8748

Abstract

COVID-19 has affected millions worldwide, causing significant morbidity and mortality. While predominantly involving the respiratory tract, SARS-CoV-2 has also caused systemic illnesses involving other sites. Liver injury due to COVID-19 has been variably reported in observational studies. It has been postulated that liver damage may be due to direct damage by SARS-CoV-2 virus or multifactorial secondary to hepatotoxic therapeutic options as well as cytokine release syndrome and sepsis-induced multiorgan dysfunction. The approach to a COVID-19 patient with liver injury requires a thorough evaluation of pattern of hepatocellular injury along with presence of underlying chronic liver disease and concurrent medications which may cause drug induced liver injury. While studies have shown uneventful recovery in the majority of mildly affected patients; severe COVID-19 associated liver injury has been associated with higher mortality, prolonged hospitalization, and greater morbidity in survivors. Furthermore, its impact on long term outcomes remains to be ascertained as recent studies report association with metabolic-fatty liver disease. This present review provides insight into the subject by describing the postulated mechanism of liver injury, its impact in the presence of pre-existing liver disease and its short- and long-term clinical implications.

Key words: COVID-19 associated liver injury; SARS-CoV-2; cytokine release syndrome.

Key points

1. COVID-19 associated liver injury can have an unpredictable course and variable manifestations.

2. The mechanisms of liver injury include direct damage by the virus, liver injury due to hepatotoxic drugs, cytokine release syndrome, and sepsis-induced multiorgan dysfunction.

3. Evaluating a COVID-19 patient with liver injury requires consideration of the pattern of hepatocellular injury, presence of underlying chronic liver disease, and concurrent medications.

4. Severe COVID-19 associated liver injury is associated with higher mortality, prolonged hospitalization, and greater morbidity in survivors.

5. Long-term clinical implications of COVID-19-associated liver injury include metabolic-associated fatty liver disease, which may have implications for overall health.

Introduction

COVID-19 has affected millions of people worldwide causing significant morbidity and mortality. As the World Health Organization declares the end of the global health emergency due to COVID-19, the world is still grappling to understand the long-term impact of the disease[1]. SARS CoV-2 is known to cause multi-organ damage including injury to lung, kidneys, neurological, cardiovascular, and liver as well as a myriad of hematological abnormalities. Liver injury was amongst the earliest recognized complications of COVID-19[2,3]. The incidence of liver injury has been reported to be between 16% to 29% and a higher prevalence was observed in hospitalized patients with COVID-19[4,5]. COVID-19 associated liver injury has been defined as any identifiable liver damage that occurs as a direct result of the COVID-19 infection or during the course of the disease or treatment, irrespective of any pre-existing comorbid or liver disease[6]. The presence and extent of liver damage that occurs is primarily measured by taking quantitative measurements of liver enzymes. There are 3 types of liver injury that are described in literature: hepatocellular, cholestatic and mixed types. An elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times greater than the upper limit of the normal value is indicative if the hepatocellular type of liver injury. Elevations in other liver enzymes such as Alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and total bilirubin that exceed two times the upper normal value are seen in the cholestatic type. The mixed type is a combination of both hepatocellular and cholestatic ranges[7]. Abnormalities with tests that assess liver function are common, but its overall impact is still under exploration. Furthermore, imaging modalities have also been utilized in identifying COVID-19 associated liver injury. These include

ultrasound (US) (main diagnostic tool for first evaluation), Computed Tomography Scan (CT) (most useful for overall abdominal assessment) and Magnetic Resonance Imaging (MRI) (most helpful in better clarifying liver changes in cases where changes on US and CT are indeterminate). Hepatomegaly, steatosis, acute hepatitis, drug induced liver injury, portal vein thrombosis and biliary involvement have all been described[8]. Liver injury has also been corroborated from liver biopsy evidence which have showed moderate microvascular steatosis and mild lobular and portal activity[9]. It is of utmost importance for physicians and researchers to analyze and assess the mechanism of liver injury and its impact on patient outcomes and disease processes. This short review focuses on the pathophysiology of COVID-19 associated liver injury and provides an overview of the management of these patients and the consequences of COVID-19 on people living with pre-existing liver disease primarily, chronic liver disease. Moreover, it elaborates on the short and long-term implications of COVID-19 associated liver injury.

Pathophysiology of COVID-19 and Liver Injury

Liver injury was first reported by Chen et al from Wuhan. They reported that 43.4% of the cases had mild to moderate elevation of ALT and AST[2]. Since then, liver injury has been observed and reported in several studies and the degree of liver damage has been associated with greater risk of progression to severe COVID-19[10,11]. The exact pathophysiology of liver damage in SARS-CoV-2 remains unclear but proposed mechanisms include direct damage to liver, drug induced, inflammatory immune response and hypoperfusion[12] (Figure 1).

Direct liver damage

SARS-CoV-2 targets the angiotensin converting enzyme 2 (ACE2) receptors which besides the lung are present in the intestinal endothelium and vascular smooth muscles[13]. ACE is also expressed by hepatocytes and cholangiocytes, although expression is higher in bile duct epithelium as compared to hepatocytes[14,15]. SARS-COV-2 can therefore cause liver injury either by binding to hepatocytes or by binding to bile duct cells, leading to upregulation of ACE2 in the liver[15]. Tian et al, however reported that inclusion bodies of the virus were not found on autopsies of COVID-19 patients[16]. This supports bile duct damage rather than hepatocyte as the cause of liver injury. Zhao et al also reported that the liver ductal cultures revealed bile duct injury as the possible cause of liver damage[17]. Liver cirrhosis can lead to increased expression of ACE2 in hepatocytes. This may result in increased invasion of hepatocytes by SARS-CoV-2 and more severe liver injury in patients with chronic liver disease[14,18].

Cytokine Release Syndrome

COVID-19 leads to a multi-system dysfunction as part of the systemic inflammatory response syndrome (SIRS). Many cytokines are released many of which are produced by the live including interleukins, tumor necrosis factors, interferons, and chemokines[19]. IL6 causes activation of T-cells, B-cell differentiation and induction of acute phase reactants in the hepatocytes[20]. The acute phase response by the liver is a protective mechanism against the pathogen[21]. The activated T-cells attack the infected cells till they are depleted. The depleted cells, when unable to control the infection activate secondary inflammatory responses leading to production of more inflammatory cytokines[22]. The excessive release of inflammatory cytokines leads to shock, multiorgan dysfunction and acute respiratory distress syndrome[23,24].

Hypoxia Reperfusion Syndrome

SARS-CoV-2 binds to several receptors in the vascular endothelium. The subsequent vascular injury leads to respiratory failure and ARDS[11]. The liver is prone to effects of hypoxemia due to its complicated vascular supply and high metabolic activity[25] . Hemodynamic instability leads to reduced flow to the liver and periphery resulting in hypoxemia causing an acute elevation of serum transaminase levels[26,27]. Persistent hypoxia due to respiratory, cardiac failure or shock causes lipid accumulation in hepatocytes progressing to cell death and apoptosis[28]. This is followed by mitochondrial damage and release of reactive oxygen species causing further damage, release of proinflammatory markers and activation of macrophages, neutrophils and platelets[28-30]. Microcirculatory disturbance leads to coagulopathy and thrombosis. Von Willebrand factor antigen correlates with severity of vascular endothelial damage and higher levels are associated with increased mortality[31].

Drug Induced Liver Injury

Drugs may be a crucial factor leading to liver injury in COVID-19. This has been supported by autopsy reports showing microvascular steatosis and hepatic inflammation[32]. Many classes of drugs have been used to treat COVID-19 since the beginning of the pandemic amongst these many are known to be hepatotoxic. Drugs used include antipyretics (e.g., Acetaminophen), antivirals (e.g., Remdesivir, Lopinavir/Ritonavir), antibiotics (e.g., Azithromycin), immunosuppressants and immunomodulators (e.g., corticosteroids, Hydroxychloroquine), Tocilizumab and herbal medicines. Besides this, many antimicrobial agents such as azoles, used for treating superimposed fungal infections such as COVID-19 associated pulmonary aspergillosis are also associated with liver enzyme dysfunction. Use of multiple drugs at the same time, possible interaction between drugs for treating COVID-19,

medications used to treat other comorbid conditions, and discontinuation of drugs being used by a patient for prior liver disorders may all contribute to liver injury[25]. There is a substantial variability of transaminitis in patients with COVID infection. Many patients receive multiple combination of drugs for the treatment; thus, it becomes difficult to evaluate the component of liver injury related to a particular drug. The drug induced liver injury may either be an intrinsic liver injury or may be an idiosyncratic one, with unspecified latency period. Thus, most drug induced liver injuries may remain as a diagnosis of exclusion unless specific testing including biopsies are performed. Many host factors including age, gender pregnancy malnutrition obesity, and comorbids like diabetes, NAFLD have been implicated as factors in idiosyncratic drug induced liver injury[33]. Among the common medications use in COVID infections are acetaminophen, NSAIDS, antivirals like Remdesivir, Lopinavir/Ritonavir, antibiotics (e.g., Azithromycin), immunosuppressants and immunomodulators (e.g., corticosteroids, Hydroxychloroquine), antibodies e.g., Tocilizumab and herbal medicines. The occurrence of DILI with acetaminophen is one of the most common drug adverse events. Mortality rates have been approximated at 0.4% in overdose patients, translating to 300 deaths annually in the United States. Although the majority of patients experience mild adverse reactions, such as hepatitis, cholestasis or asymptomatic liver enzyme elevation, APAP hepatotoxicity is generally estimated to account for approximately 48% of acute liver failure diagnoses[34-36]. DILI follows a dose dependent toxicity ranging from 0.02 up to 30%.[37]

Remdesivir, in the initial study reporting the safety of remdesivir for COVID-19 patients, conducted by Grein et al., investigated the effect of 5 to 10-days courses of remdesivir on the changes in the category of oxygen-support status in a small cohort

of 53 patients. [38] The most common adverse event in this study was increased

hepatic enzymes by an incidence of 23%. A similar pattern was replicated in the

study on 402 patients, evaluating the optimum time-course for intravenous

remdesivir, conducted by Goldman et al. In that ALT and AST elevation (7 and 6%

respectively) was reported as the most common liver adverse effects[39]. Furthermore,

in the placebo-controlled double-blinded clinical trial on a total sample of 255

patients, conducted by Wang et al., grade 1–2 Increased AST was detected as an

adverse liver effect (12% in the placebo group, 7% in remdesivir group; or 12:7%)

and grade 1–2 increased ALT led to drug discontinuation (1%)[40].

The other drug combination used for the treatment of COVD 19 infections was

lopinavir/ritonavir. A significant number of studies have reported the association of

lopinavir/ritonavir to use in COVID-19 patients with adverse liver effects. In a study

by Sun et al. on a sample of 217 patients, 63% of total adverse drug reactions

(ADRs) were associated with the use of lopinavir/ritonavir. Liver ADRs were the

second most common ADRs by a prevalence of 18%. However, the percentage of

liver ADRs due to lopinavir/ritonavir was not reported by the same study[41]. Later, Fan

et al. reported that among the 148 patients, 45 patients had normal base-line liver

functions of which 48% developed an abnormality in the liver after admission to the

hospital. They highlighted that among the patients with abnormal liver functions, a

higher proportion had used lopinavir/ritonavir (57.8%) compared to the patients with

normal liver function tests (31.3%)[42].

Hydroxychloroquine has remained in use for rheumatological disorders and

implicated in treatment for malaria, short term use is associated with very limited

adverse effects pertaining to liver injuries. However, it is implicated that when used in combination with other medications like ritonavir the adverse effects may increase. Tocilizumab Interleukin-6 (IL-6) blockers including tocilizumab and sarilumab were approved in June 2021 for the treatment of patients with moderate to severe COVID-19. There has been a noticeable difference in the peak onset times of adverse reactions between the two drugs. Some studies have reported TCZ-related DILI accounted for 67.01% the first four days after receiving TCZ therapies, and SAR-associated DILI accounted for 83.13% the first six days after receiving SAR therapies. Furthermore, it is also associated with reactivation of Hepatitis B as has been described in patients with rheumatological disorders being treated with Tocilizumab along with DMARDs [43,44].

Impact of COVID-19 on patients with pre-existing liver disorders

Impact of COVID-19 on liver function with preexisting liver disease depends on the underlying etiology and severity of underlying liver pathology. The disease presentation of COVID-19 is highly variable thus many confounding factors can be attributed increased morbidity and mortality. Multiple studies evaluated the outcomes of COVID-19 with liver pathology and found variable and conflicting results. As compared to individuals without CLD, the patients with CLD and cirrhosis may have more severe disease and a greater COVID-19-associated mortality rate. According to a system review, likelihood of COVD 19 associated severe diseases and death was 2.44 times greater in patients with CLD compared to those without underlying liver diseases[45,46].   COVID-19 can be stratified into the following groups when considering underlying liver disease.

Chronic viral hepatitis and COVID-19

Chronic viral hepatitis in the absence of chronic liver disease does not seem to affect morbidity and mortality among patients with COVID-19. However, studies have shown that COVID-19 patients with Hepatitis B (HBV) co-infection tend to have a poorer prognosis, with a 2.2-fold increased severity of COVID-19 and the in-hospital mortality rate is 6.0%. Similarly, chronic hepatitis C (HCV) patients with COVID-19 are more prone to hospitalization but not at a higher risk of death[47]. The results of a comprehensive meta-analysis by Hariyanto et al. have also shown association of viral hepatitis with severe COVID-19[48]. COVID 19 can re activate or can cause sudden increase in HBV DNA level in blood, hepatitis failure and flare of acute hepatitis in patient with chronic HBV Risk factors for HBV reactivation in patient with COVID -19 are immunosuppressive therapy including steroids, advance age, male sex, lymphopenia, and significant comorbidities (including chronic renal disease, hypertension, diabetes, and hypercholesterolemia)[49,50]. The presence of chronic HCV infection, history of HCV infection and acute liver injury are strong predictors of hospital mortality in patients with COVID -19. The mechanisms may be connected to baseline cytokine-mediated pro-inflammation and endothelial dysfunction as well as extra hepatic effects of HCV that promote ACE-2/TMPRSS mechanisms of SARS-CoV-2 viral entry[51].

Another study found that age greater than 60 years old, male gender, elevated ALT and procalcitonin levels, and high HCV viral load were all individually associated with liver damage. Additionally, ALT levels in men, an elevated HCV viral load, and a higher age above 60 were all independent risk factor for all-cause mortality[52].

It is recommended to initiate or continue anti HBV therapy in all patients with COVID-19 with concomitant or chronic HBV infections .Based on data on reactivation of HBV

with immunosuppressive therapy, studies has suggested to start antiviral prophylaxis in patient with HBV infection and receiving corticosteroids or other immunosuppressive therapy with closely monitoring HBV virological indicators and signs of liver injury[49,53].

Antiviral therapy for HCV direct acting antiviral (DAA) should be continued to maximize the sustained virological response rate with close monitoring for any adverse events because the majority of COVID-19 regimens do not have significant drug-drug interactions with agents used to treat HCV[54].

Interferon therapy for both HBV and HCV should be stopped in patients with severe COVID-19 as it is one of potent cytokine and can contribute to SARS-CoV-2 induced cytokine release syndrome[55].

Patients with viral hepatitis encountered difficulties during the pandemic as medical resources were diverted to the COVID-19 issue. Access to standard medical care for identifying early-stage hepatitis was restricted, and follow-up visits of patients with CLD were decreased because of concerns about exposure to COVID-19 infection from HCW and healthcare facilities. Essential testing available in large centers like ultrasonography and nucleic acid tests were hampered by travel restrictions, and treatment interruptions were brought on by antiviral shortages due to travel restriction and limited flight options. Infant hepatitis B vaccination rates were also similarly affected by lockdowns. Telemedicine has evolved as a valuable patient-healthcare link on a worldwide scale, but its usefulness is limited in LMIC[56-58]. Health authorities must take steps to preserve the continuity of vital programs like HCV, HBV, and TB in order to reduce the impact of future pandemic-related interruptions, especially in low-resource nations. To minimize disruptions and sustain important health services during any potential future crises, strong contingency

plans, strengthened healthcare infrastructure, and flexible service delivery methods are crucial.

Alcohol associated liver disease and COVID-19

Due to several reasons alcohol consumption was increased during COVID-19 pandemic leading to higher rates of alcoholic hepatitis. Data has suggested that greater mortality and morbidity was seen among these patients, greater incidence of acute on chronic liver failure and acute on chronic hepatitis. One postulated mechanism of injury is related to ferritin excess in patients with alcoholic hepatitis and COVID-19 infection leading to greater free radical damage to liver[59-61].

The high risk of severe COVID -19 in patients with alcohol use disorder (AUD) or alcohol induce hepatitis is secondary to presence of underlying comorbid illnesses , suppressive immunity , concomitant smoking in many cases with underlying respiratory diseases , social isolation leading to psychological stress and increased consumption of alcohol   and use of steroids or other immunosuppressive therapy for treatment of SRAS-CoV-2 infection[62].

The medications used for treatment of   alcohol used disorder (AUD) are naltrexone, nalmefene, disulfiram, acamprosate, sodium oxybate (SO), and baclofen[63]. Patients receiving treatment for alcohol use disorder (AUD), or antipsychotic should be closely monitored for drug-drug interactions as well as potential adverse reactions while receiving treatment for COVID 19.

Management of AUD or alcohol-related hepatitis has faced numerous difficulties during COVID 19 pandemic due to limited access to routine medical visits, which makes it difficult to monitor diseases and implement prompt interventions. Furthermore, forced social isolation causes psychological anguish, which could lead to increased drinking or relapse. A crucial option that enables remote patient

monitoring, consultation, and action is telemedicine. The psychological effects of isolation can also be addressed through online support groups and tele therapy[55].

Metabolic Dysfunction-associated Fatty Liver Disease (MAFLD) and severity of COVID-19

Limited data exists regarding patients with metabolically associated liver disease also called non-alcoholic fatty liver disease and COVID-19. The damage to hepatocytes seems to have a similar mechanism of injury as described with alcoholic hepatitis and COVID-19. In a retrospective study by Ji D et al. consecutive patients with COVID-19 and MAFLD were studied, and liver injury was observed in 50% on admission and 75% during hospitalization. Moreover, 33% of patients had persistent abnormal liver function from admission to the last follow-up. Patients with progressive disease were older, had higher BMI, and a higher percentage of comorbidity along with MAFLD[64]. Studies have reported increased risk of severe COVID -19 in patients with a high body mass index , a combination of metabolic risk factors with increased risks related to diabetes mellitus , hypertension, and coronary heart disease and MAFLD patients with increased noninvasive liver fibrosis scores (FIB-4 score)[65,66]. MAFLD patients had a longer viral shedding time, a higher likelihood of liver damage, and a higher probability of the disease progressing to severe COVID-19 [67].

There is a high-risk of respiratory complication related to COVID-19 in patients with MAFLD. There is little data on the effectiveness and safety of COVID-19 therapies for MAFLD patients. The choice of medication for these patients is based on variables such the severity of the illness, the ALT level, and probable interactions and medication discontinuation may be required if ALT levels are six times above average. For the treatment of MAFLD in COVID-19 cases, more research is

required[68]. It is recommended that MAFLD patients receive lifestyle counselling with an emphasis on reducing risk factors (such obesity) that indicate a poor prognosis for COVID-19.

Autoimmune liver disease and COVID-19

AILDs, which include overlapping syndromes, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), are a diverse collection of inflammatory disorders of the liver attributed to autoimmune response. Patients with AILDs are not at increased risk of acquiring COVID -19 infection as compared to the general population[69]. Autoimmune hepatitis (AIH) is a chronic inflammatory disease affecting the liver which is treated either with steroids alone or in combination with Azathioprine. Other immunosuppressive agents may be required in some cases[70,71]. Prolonged use of immunosuppression can lead to an increased risk of acquiring infections, however results of a multicenter survey in Europe suggest that AIH is not associated with an increased risk of acquiring COVID 19[69]. Furthermore, according to data compiled from three large-scale international reporting registries, European Association for the Study of the Liver supported COVID-Hep registry, the European Reference Network on Hepatological Diseases (ERN RARE-LIVER) and the American Association for the Study of Liver Diseases supported SECURE-cirrhosis registry, patients with AIH did not exhibit an elevated risk of adverse outcomes, such as hospitalization, intensive care unit stay , mortality in comparison to other causes of CLD and without any liver diseases[72].   Efe et al analyzed the factors associated with severe COVID 19 outcomes in patients with AIH[73]. They reported 37% new onset liver injury, and the use of antivirals was associated with liver injury. The rates of severe COVID 19 and mortality were similar in both AIH and non AIH CLD patients. In

another study, comparison of COVID-19 patients with AIH to those without liver disease showed a higher risk of hospitalization but a similar risk of all other outcomes, including mortality[72]. In both studies, cirrhosis was an independent predictor for severe COVID 19.

Patients with AIH are on immunosuppressive therapy for prolonged periods and several studies have shown no association between immunosuppressive therapy and severity of COVID 19. However, a subsequent study showed an increased risk of COVID 19 severity in those patients who were on steroids and azathioprine as compared to those who were not on treatment[72,74,75]. Tacrolimus and mycophenolate mofetil (MMF) were associated with similar outcomes[76]. The effect of tacrolimus and MMF on COVID 19 outcomes however requires further validation on larger cohorts, as although there are several studies [77-79] that support the association of these drugs with COVID 19 severity, there are others which show no impact of these drugs on COVID outcomes[80,81].

Vaccination against SARS COV2 is an important preventive measure for COVID 19. Effective vaccination has reduced the need for hospitalizations and mortality due to COVID 19 in the general population throughout the world[82]. Similar outcomes have been reported in patients with Chronic liver disease (CLD)[83-85]. Patients on immunosuppressive therapy and those with CLD have a low antibody response to SARS COV 2 vaccination and this has also been seen in AIH. An early third booster is recommended for these patients to maintain the antibody levels in the body[86-88]. Efe et al in their study on AIH patients with COVID 19 reported a significantly reduced risk for hospitalization, supplemental oxygen, and mortality in those who had received the SARS COV2 vaccination[89].

Among other adverse effects post SARS COV2 vaccine, autoimmune hepatitis like liver injury has also been reported[90,91]. A large case series of 87 patients describes 84% hepatocellular type injury with 57% having features of immune mediated hepatitis. Approximately half the cases received steroids. All showed completed resolution except one patient and no relapse was reported on follow up[92]. Although current recommendation is against the change of immunosuppressive treatment in patients with AIH, the available data till date supports the continuation of low dose steroids therapy to keep disease in remission[93].

Cirrhosis and COVID-19

Decompensated cirrhosis is among the independent predictors of mortality in patients with COVID-19. Attributable factors include worsening sepsis and immune dysregulation along with complications of cirrhosis. Data from two international reporting registries (SECURE-cirrhosis USA and COVID-Hep.net coordinated by University of Oxford and the European Association for the Study of the Liver) showed poorer outcomes. Hepatic decompensation during COVID-19 was strongly associated with a subsequent risk of death: 63.2% of those with new decompensation died compared to 26.2% of those without new decompensation. Notably, 24.3% of those with new hepatic decompensation had no respiratory symptoms of COVID-19 at the time of diagnosis. Hence decompensated liver disease is a significant risk factor of mortality in patients with COVID-19[94]. A multicenter study concluded that patients with cirrhosis and COVID-19 had similar mortality compared with patients with cirrhosis alone albeit higher than those with only COVID-19[95]. In another study deaths occurred in 12.2% of patients with chronic liver disease (CLD) without cirrhosis, 24% of patients with Child-Turcotte-Pugh Class

A (CTP-A) cirrhosis, 43% with CTP-B cirrhosis, and 63% with CTP-C cirrhosis. The cause of death in patients with cirrhosis was reported to be due to COVID-19 lung disease in 78.7%, cardiac-related in 4.3%, and liver-related in 12.2%[96]. However, studies have been conflicting and the pooled results have shown that CLD has played a minor role in influencing patient progression toward the severe form of the disease[97].

Cirrhosis is common and Its course is characterized by life-limiting complications such as variceal hemorrhage, ascites, hepatic encephalopathy and hepatocellular carcinoma (HCC) that require active surveillance Cirrhosis has a negative impact on COVID-19, thus management and treatment should be more rigorous in terms of medication, monitoring, and follow-up. Pandemic has severely affected management of patients with CLD and cirrhosis both with and without COVID -19. The delay has resulted in rapid progression of hepatic diseases, variceal bleed, increase incidence of hepatocellular carcinoma (HCC), delayed in procedure including liver transplant and overall mortality[98].

There should be provision of holistic, personalized and continuous care plans for patients with cirrhosis and CLD in order to avoid such complications in future crisis situations. There are new recommendations suggested by experts i.e., changing HCC surveillance from 3 months to 12 months, tele-medicine, prioritize care to high-risk patients, availability of medicine and simper surveillance techniques in community,   the effectiveness of them is yet unknown[99,100].

More clinical data is required to determine the effect of these recommendations on patient outcomes and to make sure they are appropriate given the ongoing healthcare issues.

Approach to a COVID-19 patient with liver injury

Hepatic involvement in COVID-19 can range from asymptomatic status to severe disease. Males are substantially more likely than females to get liver damage. The liver injury is predominantly found in patients with severe and critical COVID-19 and those with prior co-morbid illness like hypertension, diabetes mellitus, cardiovascular diseases, and malignancies[101] . Studies have identified several risk factors for hepatic impairment in COVID-19 patients and those include old age, obesity, severe and critical COVID-19, male gender, existing liver diseases, high C-Reactive Protein, lymphopenia and low AST/ALT ratio[102,103].

A significant proportion of patients with COVID-19 have abnormal liver biochemical tests at the time of presentation to a healthcare facility[104]. Furthermore, patients with normal liver functions can also develop hepatic injury during stay in hospital with progression in disease course[42]. Although uncommon, few cases of fulminant hepatic failure with COVID-19 have also been reported in literature[105-107]. The biochemical indicators of liver injury are elevated total bilirubin (TB), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase(GGT), alkaline phosphatase (AP), increased prothrombin time (PT) including INR and reduced levels of serum albumin in patients with COVID-19[108]. The abnormal liver function is found to be associated with critical disease, stay in high dependency unit, ICU admission, need of ventilator support, prolonged hospital stay and death[42].Among three forms of liver impairments i.e., hepatocellular injury, cholestasis and hepatocellular dysfunction, patients with hepatocellular dysfunction or mixed type have an increased likelihood of developing a serious illness[109]. Hence, monitoring of liver functions tests are warranted for patients with severe or critical COVID-19 from the time of admission.

Management

Most COVID-19 individuals experience minor, transient liver damage which returns to normal without treatment[25]. Supportive treatment is required for management of hepatic function impairment in patients with COVID-19. Detailed history and examination are required to identify any pre-existing liver diseases, prior medication, or hepatotoxic agents use. Careful monitoring of liver function tests is recommended especially in the presence of risk factors for hepatotoxicity, and previous liver diseases. In patients with severe COVID 19 and a pre-existing liver pathology, medical management should not include more than two drugs that have the potential for drug induced liver injury or drug-drug interactions. Close monitoring of the dosage and drug interaction, along with regular measurement of liver enzymes is advisable, with a prompt dose adjustment or drug discontinuation as required. Anti-inflammatory liver protection and hepatoprotective drug treatment should also be initiated as required[110]. Abnormal liver functions can persist longer than clinical recovery from acute illness which necessitates long term monitoring of liver function test in patients with severe COVID-19[25].

HCV and HBV patients should continue taking antiviral medications as discontinuation in the setting of a COVID-19 infection is not recommended in the guidelines issued by the AASLD (American Associated for the Study of Liver Disease) unless there is a pattern of worsening liver enzymes, in which case drug removal can be considered. In patients not on antiviral therapy and a history of HBV, HbsAg testing can be conducted to rule out flares[111]. In patients with liver cirrhosis; due to the high likelihood of severe complications and death; patients should continue receiving appropriate treatment[99]. Patients with comorbid conditions related to metabolic associated fatty liver disease (MAFLD) such as diabetes, dyslipidemia

and obesity, should be evaluated for liver injury as a result of MAFLD in the setting of elevated liver enzymes[25].

Changing trends in Management

The management of COVID-19 has evolved considerably over the years with the addition of newer antivirals and use of monoclonal antibodies as opposed to early in the pandemic when no approved drugs existed for this disease[112]. Furthermore, owing to vaccination, the disease manifests with relatively less severity leading to lesser and lesser requirements for salvage treatment with IL-6 antagonist Tocilizumab. This has favourable outlook for liver injury arising due to use of Tocilizumab as well as due to liver injury as a result of the disease itself. While one of the antivirals Remdesivir has been associated with drug-induced liver injury, the impact has rarely been significant enough to require discontinuation of treatment.

Biopsy findings in COVID-19 Associated Liver Injury:

Post-mortem analysis has shown that there are two possible common pathways that cause the histological changes typified in COVID associated liver injury: a post-infectious immune response and immune dysregulation[113].

Post-Infectious Immune Response:

After viral infection there may be an exaggerated immune response, and as such an increase in inflammation and is characterized by acute hepatitis and prominent bile duct injury which can lead to significant damage to the liver[114]. The histological evidence of this would be mild to severe hepatic congestion, focal confluent necrosis, hepatocyte necrosis and lobal necroinflammation underscoring the severing of the immune-mediated liver injury[115,116].

Immune Dysregulation and Susceptibility to Subsequent Infections:

Another intriguing hypothesis is that the immune dysregulation that occurs during the primary SARS-CoV-2 infection can prime the liver to react abnormally to other pathogens, such as adenoviruses. The liver expresses ACE-2 receptors, which are active binding sites for SARS-CoV-2 in the lungs and may play a role in the binding occurring in the liver as well. This binding occurs potentially more frequently and avidly on cholangiocytes rather than hepatocytes[117]. The histological manifestation of this is present in sinusoidal dilation in zone 3, patchy hepatic necrosis and the presence of cirrhosis[118]. The presence of cirrhosis may also suggest that there is further exacerbation or reactivation of underlying chronic liver diseases. Furthermore, a constellation of drug induced liver injury and ischemic liver injury due to hypoxic and shock-like states may also explain the injury that occurring to non-cholangiocytic cell types which have a far lower concentration of ACE-2 receptors[119].

Common Histological Findings:

Biopsy findings in patients diagnosed with COVID-19 associated liver injury frequently exhibit the following patterns:

1. Hepatic congestion: ranging from mild, moderate to severe, it may occur as a result of severe respiratory disease which causes right ventricular failure leading to elevated venous pressure within the liver and its vascular system[116].

2. Ischemic changes: the presence of focal confluent necrosis and hepatocyte necrosis suggest the possibility of a low oxygen state within the liver[116]. This may result because of shock, a shock-like state or chronically low oxygen saturation due to a decrease in the functionality of the lungs[118].

3. Steatosis: a very common finding on biopsies is the presence of increased fat and glycogen accumulation within the liver[120]. This may be present in a pan-

lobular pattern and suggest an additional mechanism of liver injury[115]. This may also manifest as microvascular and macrovascular steatosis[121].

Despite this wide range of abnormalities that may occur in the liver and cause injury that warrant further investigation, the routine usage of biopsies in cases of liver injury associated with COVID-19 infections is not recommended[121].

Implications of COVID-19 associated liver injury

Short term impact on patient outcomes

COVID-19 associated liver injury may be mild to severe. The prevalence of mild transaminitis has been reported between 15 to 50% with ALT/AST ratio reversal and in majority of cases is self-limiting[122]. In most patients, the ALT and AST values peak after day 6 to up to 2 weeks of illness[123]. However, studies have also reported severe liver injury with incidences reported to be higher than or equal to 70% in those patients who died of the disease[124,125]. Hence, COVID-19 associated liver injury is a marker of severity of disease or as a predictor for progression of disease whether it is a consequence of direct hepatotoxicity of SARS Cov-2 virus or a manifestation of multi-organ dysfunction. Moreover, the risk of death may be directly proportional to the degree of transaminitis[123]. In patients hospitalized with COVID-19, a moderate rise of liver function tests (LFTs) during admission were linked to a poor short-term outcome. Among patients with pre-existing liver disease, presence of cirrhosis was reported to be an independent predictor of higher 30-day mortality[126]. Furthermore, presence of liver injury in hospitalized COVID-19 patients results in prolonged length of hospital stay[127-129].

Long term impact on patient outcomes

The majority of cases of COVID-19 associated liver injury are acute, with a transient rise in biomarkers that self-resolve over a short period of time. Even in the case of acute-on-chronic liver injury the rise in hepatic biomarkers is non-permanent with the patient returning to their pre-COVID baseline soon after.

Although COVID-19 is a self-limited viral infection, its effects can be felt for weeks, and even months after resolution. The major manifestation of this is in the form of long-COVID, a constellation of signs and symptoms that affects multiple organ systems and presents after the resolution of the initial acute infection, presenting from 14-110 days post with an estimated incidence rate of 80%[130]. The major symptoms are fatigue, breathlessness, arthralgia, and chest pain however there is a multi-system involvement including but not limited to respiratory, cardiovascular, neurologic, renal, mental health and hepatic[131,132].

A study examining long term outcomes of liver function derangements in COVID-19 found that approximately 28% patients have persistent abnormalities at one year of follow-up of COVID-19 patients[133]. As opposed to this, another study from China reports persistent abnormalities in transaminase levels in 13% with majority recovering uneventfully at 12-month follow-up[134].

After the end of the acute phase, there is still an underlying risk of an increased level of hepatic biomarkers that do not return to their pre-infection baseline[135]. In a study conducted on low-risk individuals with post-COVID-19 syndrome it was found that 28% had mild injury and an increased fat accumulation in the liver which was associated with a need for hospitalization[136]. Another study looking at patients who had persisting symptoms found that there was increased liver stiffness and steatosis suggesting that there is an increased buildup of fats and fibrotic/ necrotic tissue within the liver[137].

Furthermore, there is also evidence of damage to the bile ducts, leading to post-COVID cholangiopathy. This results from ischemic changes, microthrombosis, direct liver injury, drug induced and autoimmune. Management with ursodeoxycholic acid and cholestyramine offered no significant clinical benefit[138].

Moreover, a study exploring liver fibrosis after COVID-19 using liver fibrosis index found 5% incidence of liver fibrosis in post-COVID-19 group when they followed the cohort for 3-6 months[139]. Post-acute COVID syndrome (PACS) is now a well-recognized clinical entity and is associated with several systemic manifestations including metabolic-associated fatty liver disease (MAFLD). A recent study has described an increased prevalence of this condition amongst post COVID-19 patients. The long-term consequences of MAFLD as post-COVID-19 condition remains to be ascertained and may potentially have impact on cardiovascular health outcomes[140].

Based on the understanding that long-term complications of COVID-19 on the liver are widely reported, the most potent method to ensure that further damage via fibrosis does not take place is to ensure that patients who have suffered liver injury in the acute setting, or at risk of developing long-COVID related liver injury be screened to ensure that there is a decrease in hepatic biomarkers.

Conclusion

In conclusion, COVID-19-associated liver injury can occur through multiple mechanisms and recognition and prompt management is crucial due to its significant impact on mortality and long-term morbidity. Further research and understanding of COVID-19-associated liver injury are needed to improve patient outcomes and develop effective management strategies.

References

1.   Wise J. Covid-19: WHO declares end of global health emergency. *BMJ*. 2023;381:p1041. doi:10.1136/bmj.p1041

2.   Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. May 2020;5(5):428-430. doi:10.1016/s2468-1253(20)30057-1

3.   Eastin C, Eastin T. Clinical Characteristics of Coronavirus Disease 2019 in China: Guan W, Ni Z, Hu Y, et al. N Engl J Med. 2020 Feb 28 [Online ahead of print] DOI: 10.1056/NEJMoa2002032. *J Emerg Med*. Apr 2020;58(4):711-2.

4.   Du M, Yang S, Liu M, Liu J. COVID-19 and liver dysfunction: Epidemiology, association and potential mechanisms. *Clin Res Hepatol Gastroenterol*. Feb 2022;46(2):101793. doi:10.1016/j.clinre.2021.101793

5.   Cichoż-Lach H, Michalak A. Liver injury in the era of COVID-19. *World J Gastroenterol*. Feb 7 2021;27(5):377-390. doi:10.3748/wjg.v27.i5.377

6.   Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int*. Jan 2021;41(1):20-32. doi:10.1111/liv.14730

7.   Yu D, Du Q, Yan S, et al. Liver injury in COVID-19: clinical features and treatment management. *Virology Journal*. 2021/06/09 2021;18(1):121. doi:10.1186/s12985-021-01593-1

8.   Ippolito D, Maino C, Vernuccio F, et al. Liver involvement in patients with COVID-19 infection: A comprehensive overview of diagnostic imaging features. *World J Gastroenterol*. Feb 7 2023;29(5):834-850. doi:10.3748/wjg.v29.i5.834

9.   Hu WS, Jiang FY, Shu W, Zhao R, Cao JM, Wang DP. Liver injury in COVID-19: A minireview. *World J Gastroenterol*. Dec 21 2022;28(47):6716-6731. doi:10.3748/wjg.v28.i47.6716

10.   Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. *J Hepatol*. Sep 2020;73(3):566-574. doi:10.1016/j.jhep.2020.04.006

11.   Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. Apr 30 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

12.   Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease-what we know on 1st May 2020. *Aliment Pharmacol Ther*. Jul 2020;52(2):267-275. doi:10.1111/apt.15813

13.   Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. Jun 2004;203(2):631-7. doi:10.1002/path.1570

14.   Herath CB, Warner FJ, Lubel JS, et al. Upregulation of hepatic angiotensin-converting enzyme 2 (ACE2) and angiotensin-(1-7) levels in experimental biliary fibrosis. *J Hepatol*. Sep 2007;47(3):387-95. doi:10.1016/j.jhep.2007.03.008

15.   Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: Putative mechanisms of liver involvement in COVID-19. *Liver Int*. Aug 2020;40(8):2038-2040. doi:10.1111/liv.14500

16.   Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol*. Jun 2020;33(6):1007-1014. doi:10.1038/s41379-020-0536-x

17.   Zhao B, Ni C, Gao R, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell*. Oct 2020;11(10):771-775. doi:10.1007/s13238-020-00718-6

18.   Qi X, Wang J, Li X, et al. Clinical course of COVID-19 in patients with pre-existing decompensated cirrhosis: initial report from China. *Hepatol Int*. Jul 2020;14(4):478-482. doi:10.1007/s12072-020-10051-z

19.   Fix OK, Hameed B, Fontana RJ, et al. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology*. Jul 2020;72(1):287-304. doi:10.1002/hep.31281

20.   Mojtabavi H, Saghazadeh A, Rezaei N. Interleukin-6 and severe COVID-19: a systematic review and meta-analysis. *Eur Cytokine Netw*. Jun 1 2020;31(2):44-49. doi:10.1684/ecn.2020.0448

21.   Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. May 2020;27(5):1451-1454. doi:10.1038/s41418-020-0530-3

22.   Feng G, Zheng KI, Yan QQ, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. *J Clin Transl Hepatol*. Mar 28 2020;8(1):18-24. doi:10.14218/jcth.2020.00018

23.   Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama*. May 26 2020;323(20):2052-2059. doi:10.1001/jama.2020.6775

24.   Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. *Am J Emerg Med*. Jul 2008;26(6):711-5. doi:10.1016/j.ajem.2007.10.031

25.   Li P, Liu Y, Cheng Z, Yu X, Li Y. COVID-19-associated liver injury: Clinical characteristics, pathophysiological mechanisms and treatment management. *Biomed Pharmacother*. Aug 17 2022;154:113568. doi:10.1016/j.biopha.2022.113568

26.   Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore)*. Nov 2003;82(6):392-406. doi:10.1097/01.md.0000101573.54295.bd

27.   Seeto RK, Fenn B, Rockey DC. Ischemic hepatitis: clinical presentation and pathogenesis. *Am J Med*. Aug 1 2000;109(2):109-13. doi:10.1016/s0002-9343(00)00461-7

28.   Zhang XJ, Cheng X, Yan ZZ, et al. An ALOX12-12-HETE-GPR31 signaling axis is a key mediator of hepatic ischemia-reperfusion injury. *Nat Med*. Jan 2018;24(1):73-83. doi:10.1038/nm.4451

29.   Wang X, Lei J, Li Z, Yan L. Potential Effects of Coronaviruses on the Liver: An Update. *Front Med (Lausanne)*. 2021;8:651658. doi:10.3389/fmed.2021.651658

30.   Caraceni P, Domenicali M, Vendemiale G, et al. The reduced tolerance of rat fatty liver to ischemia reperfusion is associated with mitochondrial oxidative injury. *J Surg Res*. Apr 2005;124(2):160-8. doi:10.1016/j.jss.2004.10.007

31.   Philippe A, Chocron R, Gendron N, et al. Circulating Von Willebrand factor and high molecular weight multimers as markers of endothelial injury predict COVID-19 in-hospital mortality. *Angiogenesis*. Aug 2021;24(3):505-517. doi:10.1007/s10456-020-09762-6

32.   Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. Apr 2020;8(4):420-422. doi:10.1016/s2213-2600(20)30076-x

33.   Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. Jul 2014;109(7):950-66; quiz 967. doi:10.1038/ajg.2014.131

34.   Clark R, Fisher JE, Sketris IS, Johnston GM. Population prevalence of high dose paracetamol in dispensed paracetamol/opioid prescription combinations: an observational study. *BMC Clin Pharmacol*. Jun 18 2012;12:11. doi:10.1186/1472-6904-12-11

35.   Herndon CM, Dankenbring DM. Patient perception and knowledge of acetaminophen in a large family medicine service. *J Pain Palliat Care Pharmacother*. Jun 2014;28(2):109-16. doi:10.3109/15360288.2014.908993

36.   Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. *Clin Liver Dis*. Nov 2013;17(4):587-607, viii. doi:10.1016/j.cld.2013.07.005

37.   Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update. *J Clin Transl Hepatol*. Jun 28 2016;4(2):131-42. doi:10.14218/jcth.2015.00052

38.   Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med*. Jun 11 2020;382(24):2327-2336. doi:10.1056/NEJMoa2007016

39.   Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *New England Journal of Medicine*. 2020;383(19):1827-1837. doi:10.1056/NEJMoa2015301

40.   Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. May 16 2020;395(10236):1569-1578. doi:10.1016/s0140-6736(20)31022-9

41.   Sun J, Deng X, Chen X, et al. Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System. *Clin Pharmacol Ther*. Oct 2020;108(4):791-797. doi:10.1002/cpt.1866

42.   Fan Z, Chen L, Li J, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol*. Jun 2020;18(7):1561-1566. doi:10.1016/j.cgh.2020.04.002

43.   Ridruejo E, Soza A. The liver in times of COVID-19: What hepatologists should know. *Ann Hepatol*. Jul-Aug 2020;19(4):353-358. doi:10.1016/j.aohep.2020.05.001

44.   Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proceedings of the National Academy of Sciences*. 2020;117(20):10970-10975. doi:doi:10.1073/pnas.2005615117

45.   Perreault G, Ching C, Nobel YR. COVID-19 in patients with liver disease and liver transplant: clinical implications, prevention, and management. *Therap Adv Gastroenterol*. 2023;16:17562848231188586. doi:10.1177/17562848231188586

46.   Nagarajan R, Krishnamoorthy Y, Rajaa S, Hariharan VS. COVID-19 Severity and Mortality Among Chronic Liver Disease Patients: A Systematic Review and Meta-Analysis. *Prev Chronic Dis*. Aug 25 2022;19:E53. doi:10.5888/pcd19.210228

47.   Liatsos GD. SARS-CoV-2 induced liver injury: Incidence, risk factors, impact on COVID-19 severity and prognosis in different population groups. *World J Gastroenterol*. Apr 28 2023;29(16):2397-2432. doi:10.3748/wjg.v29.i16.2397

48.   Hariyanto TI, Jodhinata C, Halim DA, Kurniawan A. Association between viral hepatitis and increased risk of severe coronavirus disease 2019 (COVID-19) outcome: a systematic review and meta-analysis. *Gastroenterol Hepatol Bed Bench*. Winter 2022;15(1):9-14.

49.   Sagnelli C, Montella L, Grimaldi P, et al. COVID-19 as Another Trigger for HBV Reactivation: Clinical Case and Review of Literature. *Pathogens*. 2022;11(7):816.

50.   Rodríguez-Tajes S, Miralpeix A, Costa J, et al. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. *J Viral Hepat*. Jan 2021;28(1):89-94. doi:10.1111/jvh.13410

51.   Ronderos D, Omar AMS, Abbas H, et al. Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality. *World journal of clinical cases*. Oct 16 2021;9(29):8749-8762. doi:10.12998/wjcc.v9.i29.8749

52.   Cerbu B, Pantea S, Bratosin F, et al. Liver Impairment and Hematological Changes in Patients with Chronic Hepatitis C and COVID-19: A Retrospective Study after One Year of Pandemic. *Medicina (Kaunas)*. Jun 10 2021;57(6)doi:10.3390/medicina57060597

53.   Yip TC, Gill M, Wong GL, Liu K. Management of hepatitis B virus reactivation due to treatment of COVID-19. *Hepatol Int*. Apr 2022;16(2):257-268. doi:10.1007/s12072-022-10306-x

54.   Wong GL, Wong VW, Thompson A, et al. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. *Lancet Gastroenterol Hepatol*. Aug 2020;5(8):776-787. doi:10.1016/s2468-1253(20)30190-4

55.   Hamid S, Alvares Da Silva MR, Burak KW, et al. WGO Guidance for the Care of Patients with COVID-19 and Liver Disease. 2021. doi:10.1097/MCG.0000000000001459 https://hdl.handle.net/2123/25300

56.   Pley CM, McNaughton AL, Matthews PC, Lourenço J. The global impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of hepatitis B virus (HBV) infection. *BMJ Glob Health*. Jan 2021;6(1)doi:10.1136/bmjgh-2020-004275

57.   Rehman ST, Rehman H, Abid S. Impact of coronavirus disease 2019 on prevention and elimination strategies for hepatitis B and hepatitis C. *World J Hepatol*. Jul 27 2021;13(7):781-789. doi:10.4254/wjh.v13.i7.781

58.   Ismail Z, Aborode AT, Oyeyemi AA, et al. Impact of COVID-19 pandemic on viral hepatitis in Africa: Challenges and way forward. *Int J Health Plann Manage*. Jan 2022;37(1):547-552. doi:10.1002/hpm.3317

59.   Julien J, Ayer T, Tapper EB, Barbosa C, Dowd WN, Chhatwal J. Effect of increased alcohol consumption during COVID-19 pandemic on alcohol-associated liver disease: A modeling study. *Hepatology*. Jun 2022;75(6):1480-1490. doi:10.1002/hep.32272

60.   Cholankeril G, Goli K, Rana A, et al. Impact of COVID-19 Pandemic on Liver Transplantation and Alcohol-Associated Liver Disease in the USA. *Hepatology*. Dec 2021;74(6):3316-3329. doi:10.1002/hep.32067

61.   Testino G, A DIB, Fagoonee S, Pellicano R. SARS-CoV-2, alcohol consumption and liver injury. *Minerva Med*. Apr 2022;113(2):333-342. doi:10.23736/s0026-4806.21.07809-5

62.   Da BL, Im GY, Schiano TD. Coronavirus Disease 2019 Hangover: A Rising Tide of Alcohol Use Disorder and Alcohol-Associated Liver Disease. *Hepatology*. Sep 2020;72(3):1102-1108. doi:10.1002/hep.31307

63.   Antonelli M, Ferrulli A, Sestito L, et al. Alcohol addiction - the safety of available approved treatment options. *Expert Opin Drug Saf*. Feb 2018;17(2):169-177. doi:10.1080/14740338.2018.1404025

64.   Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol*. Aug 2020;73(2):451-453. doi:10.1016/j.jhep.2020.03.044

65.   Targher G, Mantovani A, Byrne CD, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut*. Aug 2020;69(8):1545-1547. doi:10.1136/gutjnl-2020-321611

66.   Xu L, Mao Y, Chen G. Risk factors for 2019 novel coronavirus disease (COVID-19) patients progressing to critical illness: a systematic review and meta-analysis. *Aging (Albany NY)*. Jun 23 2020;12(12):12410-12421. doi:10.18632/aging.103383

67.   Huang R, Zhu L, Wang J, et al. Clinical Features of Patients With COVID-19 With Nonalcoholic Fatty Liver Disease. *Hepatol Commun*. Dec 2020;4(12):1758-1768. doi:10.1002/hep4.1592

68.   Jeeyavudeen MS, Chaudhari R, Pappachan JM, Fouda S. Clinical implications of COVID-19 in patients with metabolic-associated fatty liver disease. *World J Gastroenterol*. Jan 21 2023;29(3):487-502. doi:10.3748/wjg.v29.i3.487

69.   Zecher BF, Buescher G, Willemse J, et al. Prevalence of COVID-19 in patients with autoimmune liver disease in Europe: A patient-oriented online survey. *United European Gastroenterol J*. Sep 2021;9(7):797-808. doi:10.1002/ueg2.12100

70.   Nur Dagli S, Efe C. Coronavirus disease 2019 (COVID-19) in autoimmune hepatitis. *Hepatol Forum*. May 2022;3(2):68-70. doi:10.14744/hf.2022.2022.0012

71.   Mack CL, Adams D, Assis DN, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology*. Aug 2020;72(2):671-722. doi:10.1002/hep.31065

72.   Marjot T, Buescher G, Sebode M, et al. SARS-CoV-2 infection in patients with autoimmune hepatitis. *J Hepatol*. Jun 2021;74(6):1335-1343. doi:10.1016/j.jhep.2021.01.021

73.   Efe C, Dhanasekaran R, Lammert C, et al. Outcome of COVID-19 in Patients With Autoimmune Hepatitis: An International Multicenter Study. *Hepatology*. 2021;73(6):2099-2109. doi:10.1002/hep.31797

74.   Efe C, Dhanasekaran R, Lammert C, et al. Outcome of COVID-19 in Patients With Autoimmune Hepatitis: An International Multicenter Study. *Hepatology*. Jun 2021;73(6):2099-2109. doi:10.1002/hep.31797

75.   Gerussi A, Rigamonti C, Elia C, et al. Coronavirus Disease 2019 in Autoimmune Hepatitis: A Lesson From Immunosuppressed Patients. *Hepatol Commun*. Sep 2020;4(9):1257-1262. doi:10.1002/hep4.1557

76.   Efe C, Lammert C, Taşçılar K, et al. Effects of immunosuppressive drugs on COVID-19 severity in patients with autoimmune hepatitis. *Liver Int*. Mar 2022;42(3):607-614. doi:10.1111/liv.15121

77.   Rabiee A, Sadowski B, Adeniji N, et al. Liver Injury in Liver Transplant Recipients With Coronavirus Disease 2019 (COVID-19): U.S. Multicenter Experience. *Hepatology*. Dec 2020;72(6):1900-1911. doi:10.1002/hep.31574

78.   Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol*. Nov 2020;5(11):1008-1016. doi:10.1016/s2468-1253(20)30271-5

79.   Belli LS, Fondevila C, Cortesi PA, et al. Protective Role of Tacrolimus, Deleterious Role of Age and Comorbidities in Liver Transplant Recipients With Covid-19: Results From the ELITA/ELTR Multi-center European Study. *Gastroenterology*. Mar 2021;160(4):1151-1163.e3. doi:10.1053/j.gastro.2020.11.045

80.   Colmenero J, Rodríguez-Perálvarez M, Salcedo M, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol*. Jan 2021;74(1):148-155. doi:10.1016/j.jhep.2020.07.040

81.   Nørgård BM, Nielsen J, Knudsen T, et al. Hospitalization for COVID-19 in patients treated with selected immunosuppressant and immunomodulating agents, compared to the general population: A Danish cohort study. *Br J Clin Pharmacol*. Apr 2021;87(4):2111-2120. doi:10.1111/bcp.14622

82.   Khandker SS, Godman B, Jawad MI, et al. A Systematic Review on COVID-19 Vaccine Strategies, Their Effectiveness, and Issues. *Vaccines (Basel)*. Nov 24 2021;9(12)doi:10.3390/vaccines9121387

83.   John BV, Deng Y, Scheinberg A, et al. Association of BNT162b2 mRNA and mRNA-1273 Vaccines With COVID-19 Infection and Hospitalization Among Patients With Cirrhosis. *JAMA Intern Med*. Oct 1 2021;181(10):1306-1314. doi:10.1001/jamainternmed.2021.4325

84.   Moon AM, Webb GJ, García-Juárez I, et al. SARS-CoV-2 Infections Among Patients With Liver Disease and Liver Transplantation Who Received COVID-19 Vaccination. *Hepatol Commun*. Apr 2022;6(4):889-897. doi:10.1002/hep4.1853

85.   John BV, Deng Y, Schwartz KB, et al. Postvaccination COVID-19 infection is associated with reduced mortality in patients with cirrhosis. *Hepatology*. Jul 2022;76(1):126-138. doi:10.1002/hep.32337

86.   Duengelhoef P, Hartl J, Rüther D, et al. SARS-CoV-2 vaccination response in patients with autoimmune hepatitis and autoimmune cholestatic liver disease. *United European Gastroenterol J*. Apr 2022;10(3):319-329. doi:10.1002/ueg2.12218

87.   Galmiche S, Luong Nguyen LB, Tartour E, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. *Clin Microbiol Infect*. Feb 2022;28(2):163-177. doi:10.1016/j.cmi.2021.09.036

88.   Chauhan M, Nzeako I, Li F, Thuluvath PJ. Antibody response after a booster dose of SARS-CoV-2 vaccine in liver transplant recipients and those with chronic liver diseases. *Ann Hepatol*. Jul-Aug 2022;27(4):100702. doi:10.1016/j.aohep.2022.100702

89.   Efe C, Taşçılar K, Gerussi A, et al. SARS-CoV-2 vaccination and risk of severe COVID-19 outcomes in patients with autoimmune hepatitis. *J Autoimmun*. Oct 2022;132:102906. doi:10.1016/j.jaut.2022.102906

90.   Shroff H, Satapathy SK, Crawford JM, Todd NJ, VanWagner LB. Liver injury following SARS-CoV-2 vaccination: A multicenter case series. *J Hepatol*. Jan 2022;76(1):211-214. doi:10.1016/j.jhep.2021.07.024

91.   Bril F, Al Diffalha S, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty? *J Hepatol*. Jul 2021;75(1):222-224. doi:10.1016/j.jhep.2021.04.003

92.   Efe C, Kulkarni AV, Terziroli Beretta-Piccoli B, et al. Liver injury after SARS-CoV-2 vaccination: Features of immune-mediated hepatitis, role of corticosteroid therapy and outcome. *Hepatology*. Dec 2022;76(6):1576-1586. doi:10.1002/hep.32572

93.   Floreani A, De Martin S. COVID-19 and Autoimmune Liver Diseases. *J Clin Med*. May 10 2022;11(10)doi:10.3390/jcm11102681

94.   Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *Journal of Hepatology*. 2021;74(3):567-577. doi:10.1016/j.jhep.2020.09.024

95.   Bajaj JS, Garcia-Tsao G, Biggins SW, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19

alone: multicentre matched cohort. *Gut*. Mar 2021;70(3):531-536. doi:10.1136/gutjnl-2020-322118

96.   Moon AM, Webb GJ, Aloman C, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. *J Hepatol*. Sep 2020;73(3):705-708. doi:10.1016/j.jhep.2020.05.013

97.   Lippi G, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *European journal of gastroenterology & hepatology*. Jan 2021;33(1):114-115. doi:10.1097/meg.0000000000001742

98.   Tapper EB, Asrani SK. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. *J Hepatol*. Aug 2020;73(2):441-445. doi:10.1016/j.jhep.2020.04.005

99.   Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP reports : innovation in hepatology*. Jun 2020;2(3):100113. doi:10.1016/j.jhepr.2020.100113

100.   Wang JH, Chang KC, Kee KM, et al. Hepatocellular carcinoma surveillance at 4- vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. *Am J Gastroenterol*. Mar 2013;108(3):416-24. doi:10.1038/ajg.2012.445

101.   Shen JX, Zhuang ZH, Zhang QX, et al. Risk Factors and Prognosis in Patients with COVID-19 and Liver Injury: A Retrospective Analysis. *J Multidiscip Healthc*. 2021;14:629-637. doi:10.2147/jmdh.S293378

102.   Yu D, Du Q, Yan S, et al. Liver injury in COVID-19: clinical features and treatment management. *Virol J*. Jun 9 2021;18(1):121. doi:10.1186/s12985-021-01593-1

103.   Chen F, Chen W, Chen J, et al. Clinical features and risk factors of COVID-19-associated liver injury and function: A retrospective analysis of 830 cases. *Ann Hepatol*. Mar-Apr 2021;21:100267. doi:10.1016/j.aohep.2020.09.011

104.   Xing QQ, Dong X, Ren YD, et al. Liver Chemistries in Patients With COVID-19 Who Were Discharged Alive or Died: A Meta-analysis. *Hepatol Commun*. Jan 2021;5(1):12-23. doi:10.1002/hep4.1585

105.   Ding ZY, Li GX, Chen L, et al. Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol*. Jun 2021;74(6):1295-1302. doi:10.1016/j.jhep.2020.12.012

106.   Aldossary B, Hassan A, Moussa M, Alsaif HS, Alfaraj D. Fulminant hepatic failure in a patient testing re-positive for SARS-CoV-2: a case report. *International Journal of Emergency Medicine*. 2021/04/21 2021;14(1):24. doi:10.1186/s12245-021-00349-6

107.   Melquist S, Estepp K, Aleksandrovich Y, et al. COVID-19 presenting as fulminant hepatic failure: A case report. *Medicine (Baltimore)*. Oct 23 2020;99(43):e22818. doi:10.1097/md.0000000000022818

108.   Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated Liver Biochemistries in Hospitalized Chinese Patients With Severe COVID-19: Systematic Review and Meta-analysis. *Hepatology*. Apr 2021;73(4):1521-1530. doi:10.1002/hep.31472

109.   Mohammed SA, Eid KM, Anyiam FE, et al. Liver injury with COVID-19: laboratory and histopathological outcome-systematic review and meta-analysis. *Egypt Liver J*. 2022;12(1):9. doi:10.1186/s43066-022-00171-6

110.   Sodeifian F, Seyedalhosseini ZS, Kian N, et al. Drug-Induced Liver Injury in COVID-19 Patients: A Systematic Review. *Front Med (Lausanne)*. 2021;8:731436. doi:10.3389/fmed.2021.731436

111.   Diseases AAftSoL. AASLD EXPERT PANEL CONSENSUS STATEMENT: COVID-19 CLINICAL BEST PRACTICE ADVICE FOR HEPATOLOGY AND LIVER TRANSPLANT PROVIDERS. Accessed 21 May 2023, 2023. https://www.aasld.org/sites/default/files/2022-10/AASLD%20COVID-19%20Guidance%20Document%2010.06.2022F.pdf

112.   Yapali S. What hepatologists need to know about COVID-19? *Hepatol Forum*. May 2020;1(2):41-43. doi:10.14744/hf.2020.2020.0011

113.   Alexander EC, Deep A. Characterization of a Hepatitis Outbreak in Children, 2021 to 2022. *JAMA Netw Open*. Oct 3 2022;5(10):e2237091. doi:10.1001/jamanetworkopen.2022.37091

114.   Kleiner DE. Liver Biopsy Shines a Light on COVID-19-Related Liver Injury. *Cell Mol Gastroenterol Hepatol*. 2021;11(3):881-882. doi:10.1016/j.jcmgh.2020.10.003

115.   Lagana SM, Kudose S, Iuga AC, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol*. Nov 2020;33(11):2147-2155. doi:10.1038/s41379-020-00649-x

116.   Beigmohammadi MT, Jahanbin B, Safaei M, et al. Pathological Findings of Postmortem Biopsies From Lung, Heart, and Liver of 7 Deceased COVID-19 Patients. *Int J Surg Pathol*. Apr 2021;29(2):135-145. doi:10.1177/1066896920935195

117.   Chai X, Hu L, Zhang Y, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. *bioRxiv*. 2020:2020.02.03.931766. doi:10.1101/2020.02.03.931766

118.   Vishwajit D, Rohini M, Ashutosh K, Chiman K, Khursheed R. Histopathological observations in COVID-19: a systematic review. *Journal of Clinical Pathology*. 2021;74(2):76. doi:10.1136/jclinpath-2020-206995

119.   Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology*. 2004;203(2):631-637. doi:https://doi.org/10.1002/path.1570

120.   Li Y, Xiao S-Y. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *Journal of Medical Virology*. 2020;92(9):1491-1494. doi:https://doi.org/10.1002/jmv.25973

121.   Hamid S, Alvares da Silva MR, Burak KW, et al. WGO Guidance for the Care of Patients With COVID-19 and Liver Disease. *J Clin Gastroenterol*. Jan 2021;55(1):1-11. doi:10.1097/mcg.0000000000001459

122.   D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl*. Jun 2020;26(6):832-834. doi:10.1002/lt.25756

123.   Shafran N, Issachar A, Shochat T, Shafran IH, Bursztyn M, Shlomai A. Abnormal liver tests in patients with SARS-CoV-2 or influenza - prognostic similarities and temporal disparities. *JHEP reports : innovation in hepatology*. Jun 2021;3(3):100258. doi:10.1016/j.jhepr.2021.100258

124.   Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. May 2020;40(5):998-1004. doi:10.1111/liv.14435

125.   Amin M. COVID-19 and the liver: overview. *European journal of gastroenterology & hepatology*. Mar 1 2021;33(3):309-311. doi:10.1097/meg.0000000000001808

126.   Grgurevic I, Lucijanić M, Pastrovic F, et al. Short-term outcomes of patients with chronic liver disease hospitalised with COVID-19. *Internal medicine journal*. May 12 2022;doi:10.1111/imj.15817

127.	Zhou F, Xia J, Yuan HX, Sun Y, Zhang Y. Liver injury in COVID-19: Known and unknown. *World journal of clinical cases*. Jul 6 2021;9(19):4980-4989. doi:10.12998/wjcc.v9.i19.4980

128.	Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. *Liver Int*. Jun 2020;40(6):1321-1326. doi:10.1111/liv.14449

129.	Youssef M, M HH, Attia AS, et al. COVID-19 and liver dysfunction: A systematic review and meta-analysis of retrospective studies. *J Med Virol*. Oct 2020;92(10):1825-1833. doi:10.1002/jmv.26055

130.	Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep*. Aug 9 2021;11(1):16144. doi:10.1038/s41598-021-95565-8

131.	Michelen M, Manoharan L, Elkheir N, et al. Characterising long COVID: a living systematic review. *BMJ Glob Health*. Sep 2021;6(9)doi:10.1136/bmjgh-2021-005427

132.	Akbarialiabad H, Taghrir MH, Abdollahi A, et al. Long COVID, a comprehensive systematic scoping review. *Infection*. Dec 2021;49(6):1163-1186. doi:10.1007/s15010-021-01666-x

133.	Zhu X, Wang J, Du J, et al. Changes in Serum Liver Function for Patients with COVID-19: A 1-Year Follow-Up Study. *Infect Drug Resist*. 2022;15:1857-1870. doi:10.2147/idr.S356181

134.	Liao X, Li D, Ma Z, et al. 12-Month Post-Discharge Liver Function Test Abnormalities Among Patients With COVID-19: A Single-Center Prospective Cohort Study. *Front Cell Infect Microbiol*. 2022;12:864933. doi:10.3389/fcimb.2022.864933

135.	Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *Bmj*. May 19 2021;373:n1098. doi:10.1136/bmj.n1098

136.	Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*. Mar 30 2021;11(3):e048391. doi:10.1136/bmjopen-2020-048391

137.	Bende F, Tudoran C, Sporea I, et al. A Multidisciplinary Approach to Evaluate the Presence of Hepatic and Cardiac Abnormalities in Patients with Post-Acute COVID-19 Syndrome-A Pilot Study. *J Clin Med*. Jun 6 2021;10(11)doi:10.3390/jcm10112507

138.	Veerankutty FH, Sengupta K, Vij M, et al. Post-COVID-19 cholangiopathy: Current understanding and management options. *World J Gastrointest Surg*. May 27 2023;15(5):788-798. doi:10.4240/wjgs.v15.i5.788

139.	Kolesova O, Vanaga I, Laivacuma S, et al. Intriguing findings of liver fibrosis following COVID-19. *BMC Gastroenterol*. Oct 11 2021;21(1):370. doi:10.1186/s12876-021-01939-7

140.	Milic J, Barbieri S, Gozzi L, et al. Metabolic-Associated Fatty Liver Disease Is Highly Prevalent in the Postacute COVID Syndrome. *Open Forum Infect Dis*. Mar 2022;9(3):ofac003. doi:10.1093/ofid/ofac003
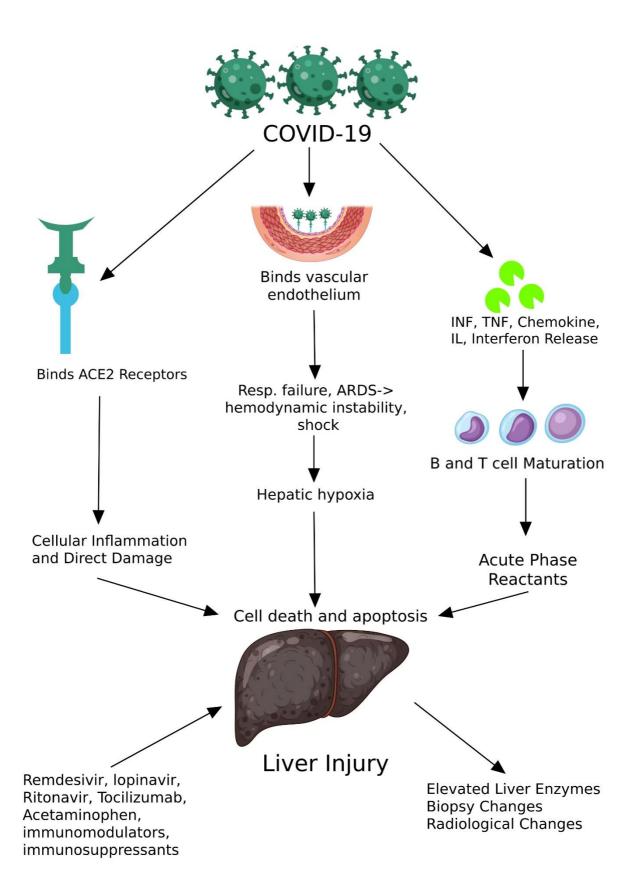
Figure 1: Pathophysiology of COVID-19 Associated Liver Injury