به نام خدا

Liver and covid 19

- دکتر نوشین سجادی
- فوق تخصص گوارش و کبد کودکان

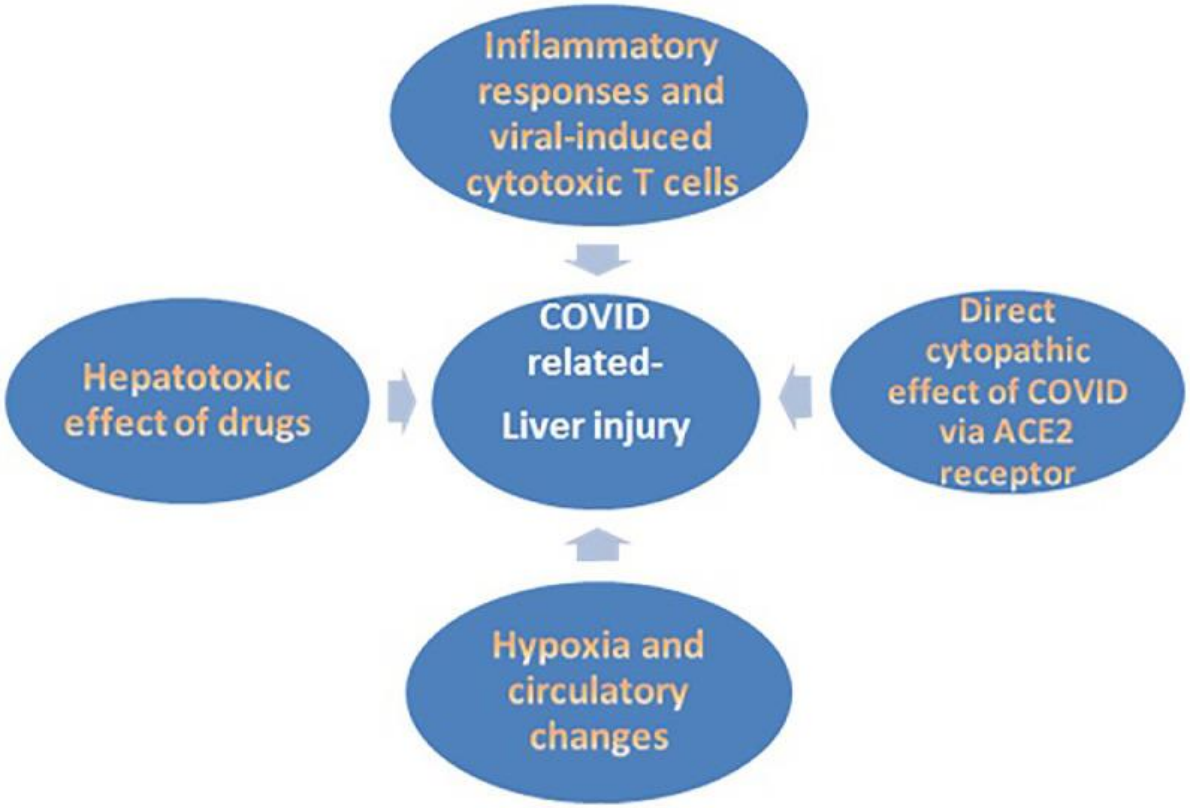
1- liver in covid 19

2-Liver disease and covid 19

ADULTS vs CHILDREN

Hepatic involvement in COVID-19 could be related to :

- The direct cytopathic effect of the virus,
- An uncontrolled immune reaction, exaggerated immune responses/systemic inflammatory response syndrome (SIRS)
- Sepsis/hypoxia
- Drug-induced liver injury
- Coagulopathy
- Gut microbiota


Inflammatory responses and viral-induced cytotoxic T cells
Hepatotoxic effect of drugs
COVID related-
Liver injury
Direct cytopathic effect of COVID via ACE2 receptor
Hypoxia and circulatory changes

Angiotensin-converting enzyme 2 receptors

- Angiotensin-converting enzyme 2 (ACE2) receptors provide a gateway for viral entry, and its tissue distribution determines the pattern of viral tropism.

- There is high expression of ACE2 on cholangiocytes (epithelial cells of the bile duct) and low expression on hepatocytes, Kupffer cells (liver macrophages), and endothelial cells. Levels of expression on bile ducts are similar to type II alveolar cells.

Direct viral cytotoxicity

- ACE-2

- Direct viral cytotoxicity gives rise to steatohepatitis by interfering with lipogenesis and in turn, may worsen chronic liver diseases such as nonalcoholic fatty liver disease (NAFLD) and alcoholic hepatitis.

Immune-mediated effects

- An exaggerated inflammatory response in COVID-19 leads to lymphocyte activation, neutrophilia, and an increase in C-reactive protein (CRP) and inflammatory cytokines
- A CRP $ 20 mg/L and a lymphocyte count , 1.1 3 109/L are independent risk factors for liver injury. Lymphopenia is noted in 63–70.3% of COVID-19 patients.
- Postmortem liver histology shows microvesicular steatosis and T cell accumulation, pointing to the presence of immune mediated damage

Hypoxia-related effects

- Liver hypoxia (because of microvascular thrombosis and gas exchange defects secondary to lung injury) may cause hepatic damage.
- Ischemic injury to the gut with resulting intestinal endotoxemia, and activation of the sympathetic nervous and adrenocortical systems may further contribute to liver damage.
- Furthermore:
- COVID-19-induced myocardial dysfunction can potentially give rise to right heart failure, adding to the existing damage, and worsening ischemic liver injury.
- Elevated transaminases in the context of respiratory failure, shock, and heart failure in severe COVID-19 may be indicators of this pathophysiological mechanism

Drug-related cytotoxicity

- As most COVID-19 patients have fever, antipyretics containing acetaminophen are frequently used. Higher doses of this medication are known to cause liver damage.
- Many antiviral drugs are administered (alone or in combination) and some of them may have adverse effects on the liver .
- It should be noted that some of the medications are no longer in use for COVID-19 in current clinical practice. Lopinavir/ritonavir increases the odds of liver injury by **fourfold**.
- Thus close monitoring is needed in such patients especially when abnormal liver function tests (LFTs) have been observed at admission.

TABLE 2

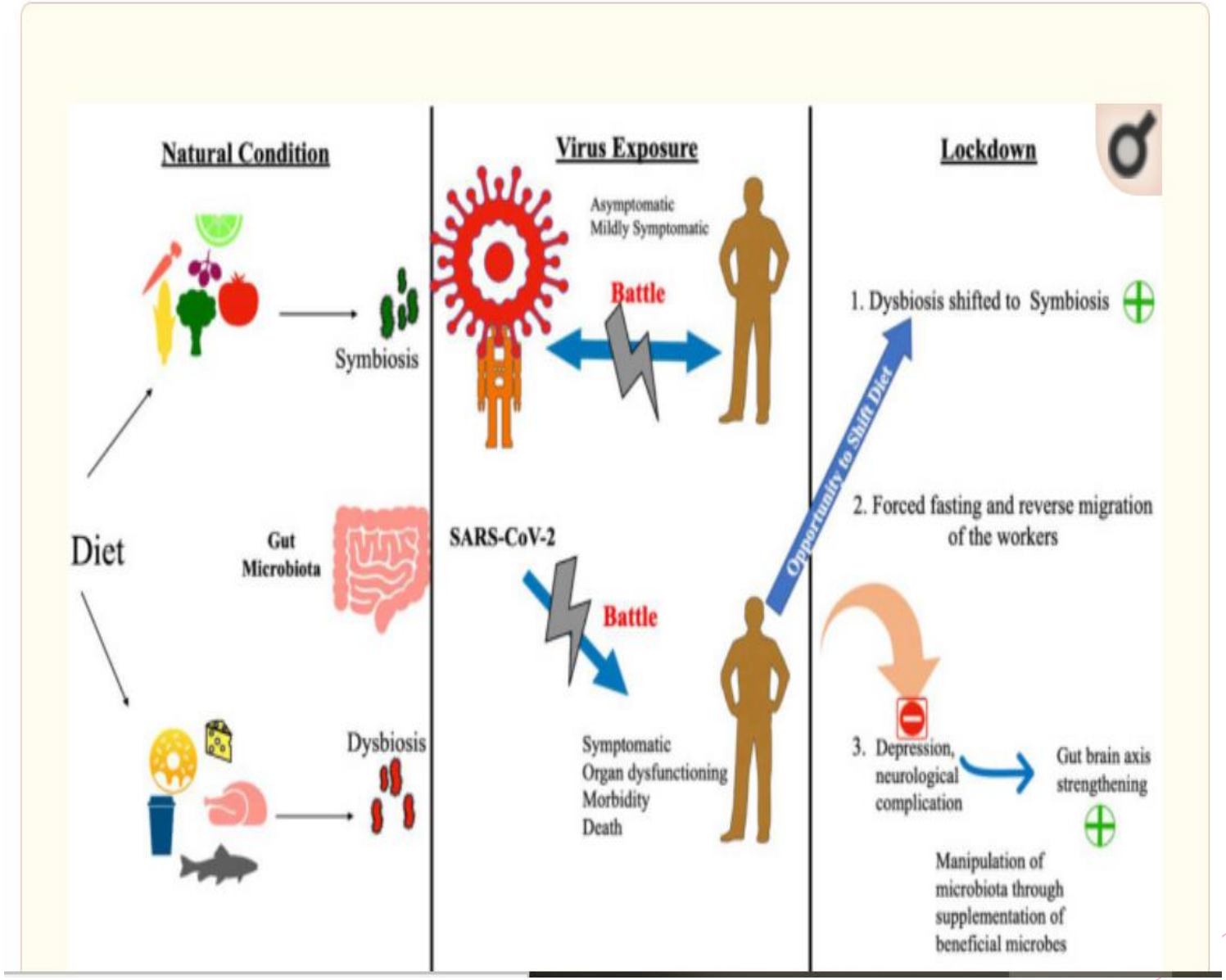
Potential liver side effects of currently and previously used medications in COVID-19

Class	Drug	Dosage	Administration	Liver side effects	References
Antivirals	Remdesivir (In phase 3 clinical trials)	Loading dose 200 mg over 30–120 minutes on day 1 followed by 100 mg once daily for remaining 4/9 days Not needing invasive mechanical ventilation/ECMO: for 5 days Needs mechanical ventilation or ECMO for 10 days	Intravenous	1–10%—liver enzyme derangement, hyperbilirubinemia	31,32,33,34
	Paxlovid ((PF-07321332 150 mg and ritonavir 100 mg)	300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days	Oral	May cause liver damage because of ritonavir. No dosage adjustment is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.	47
	Molnupiravir	800 mg (administered as four 200 mg capsules) taken orally every 12 hours with or without food for 5 days	Oral	N/A	48
	Lopinavir/ ritonavir (LPV/r) (Kaletra)	400/100 mg twice daily or 800/200 mg once daily for 14 days.	Oral (administer with or without food)	1–10%—hepatic disorders, cholangitis, hyperbilirubinemia	35
	Ribavirin (In phase 2 clinical trials)	400 mg twice daily for 14 days (in clinical trials)—dosing not defined	Oral (administer with food)	0.1–1%—Hepatic disorders Less than 0.1%—Cholangitis, hepatic failure	36
	Darunavir	1 pill of DRV/c (a single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat) per day for 5 days	Oral	Moderate to severe elevations in serum aminotransferase levels (> 5 × ULN) in 3–10% of patients overall	37
	Favipiravir	1,800 mg twice daily on day 1 followed by 800 mg twice daily on days 2 to a maximum of 14 days	Oral	Liver enzyme derangement (2%)	38

Immunomodulatory drugs	Tocilizumab	4–8 mg/kg (maximum 800 mg) over 1 hour; or 400 mg once Consider an additional dose 8–12 hours later if continued clinical deterioration (maximum of 2 doses)	Intravenous	Frequency not known—Hepatic disorders	31
	Interferon α/β	INF-β-1b 0.25 mg alternated for 3 days (in clinical trial)—dosing not established	Subcutaneous injection	0.1–1%—Hepatic disorders, autoimmune hepatitis	31
	Baricitinib (completed clinical trial)	4 mg once daily Baricitinib + antiviral therapy administration for 2 weeks	Oral	Frequency not known—Abnormal liver enzymes	39,4
	Imatinib	400 mg daily for 14 days	Oral	Common elevations in serum aminotransferase levels mild elevations in serum bilirubin can occur. These abnormalities are usually mild, asymptomatic, and resolve despite continuing therapy. Linked to rare instances of clinically apparent acute liver injury with jaundice.	41,4
Antiparasitic	Chloroquine	500 mg twice/day for 10 days.	Oral (administer with food)	Less than 0.1%—Hepatitis	(33
	Hydroxychloroquine	Loading dose of 400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days.	Oral (administer with food)	Frequency not known—Acute hepatic failure	31,4
Steroids	Dexamethasone	6mg daily for 7–10 days	Oral	Frequency not known—Acute hepatic failure	44,4
Antibiotic	Azithromycin	NA	NA	Low rate of acute, transient, and asymptomatic elevation in serum aminotransferases which occurs in 1–2% of patients treated for short periods, and a somewhat higher proportion of patients given azithromycin long term. Rarely cause clinically	46

Gut microbiota

- Recent studies on gut microbiota have suggested an alteration in intestinal microbiota composition (i.e., dysbiosis) contributes to different immune-mediated inflammatory diseases.
- Similarly, in COVID-19, gut microbiota dysbiosis might play an important role in determining the clinical outcome of patients with underlying comorbid conditions such as diabetes, hypertension, and obesity .
- As diet plays a critical role in modulating the gut microbiota, there has been increased interest in evaluating the health benefits and disease-preventing properties of diet and dietary habits and their association with favorable patient outcomes.


Natural Condition
Virus Exposure
Lockdown
Asymptomatic
Mildly Symptomatic
Battle
Symbiosis
1. Dysbiosis shifted to Symbiosis
Opportunity to Shift Diet
Diet
Gut
Microbiota
SARS-CoV-2
2. Forced fasting and reverse migration of the workers
Battle
Dysbiosis
Symptomatic
Organ dysfunctioning
Morbidity
Death
3. Depression, neurological complication
Gut brain axis strengthening
Manipulation of microbiota through supplementation of beneficial microbes

Coagulopathy

- Severe COVID-19 illness is associated with intense inflammation, leading to high rates of thrombotic complications that increase morbidity and mortality.
- Markedly elevated levels of D-dimer with normal fibrinogen levels are the hallmark laboratory findings of severe COVID-19- associated coagulopathy.

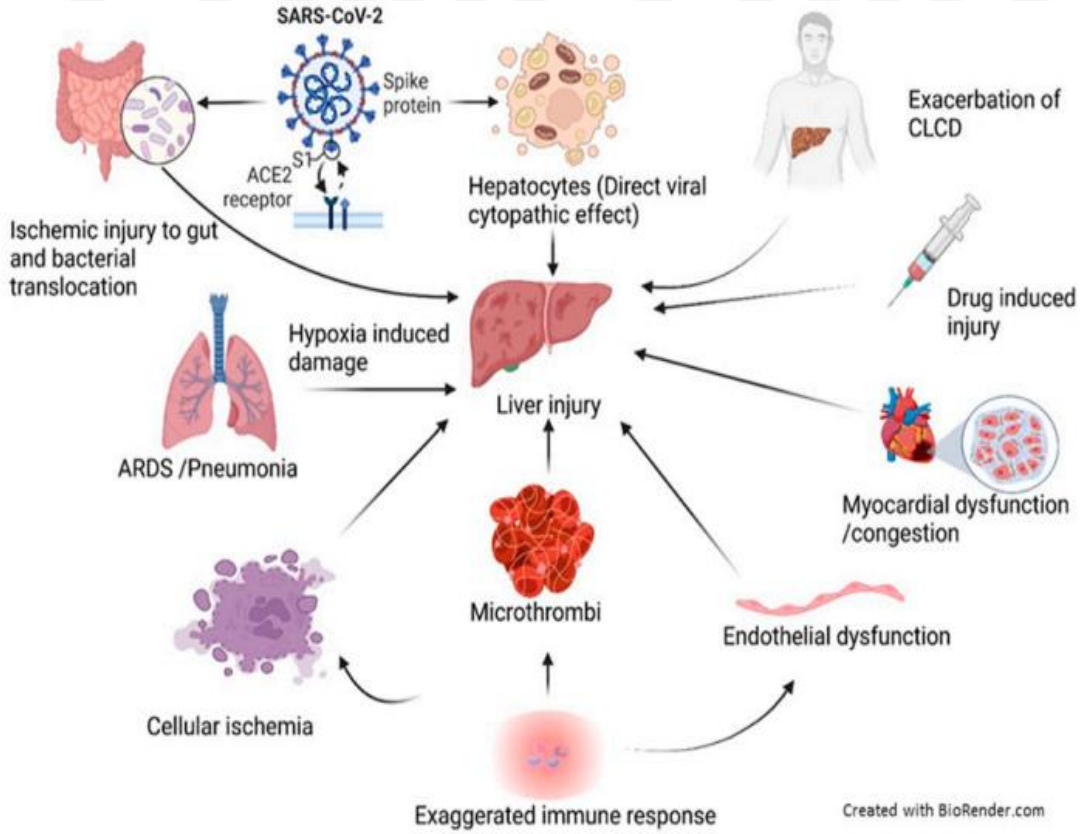


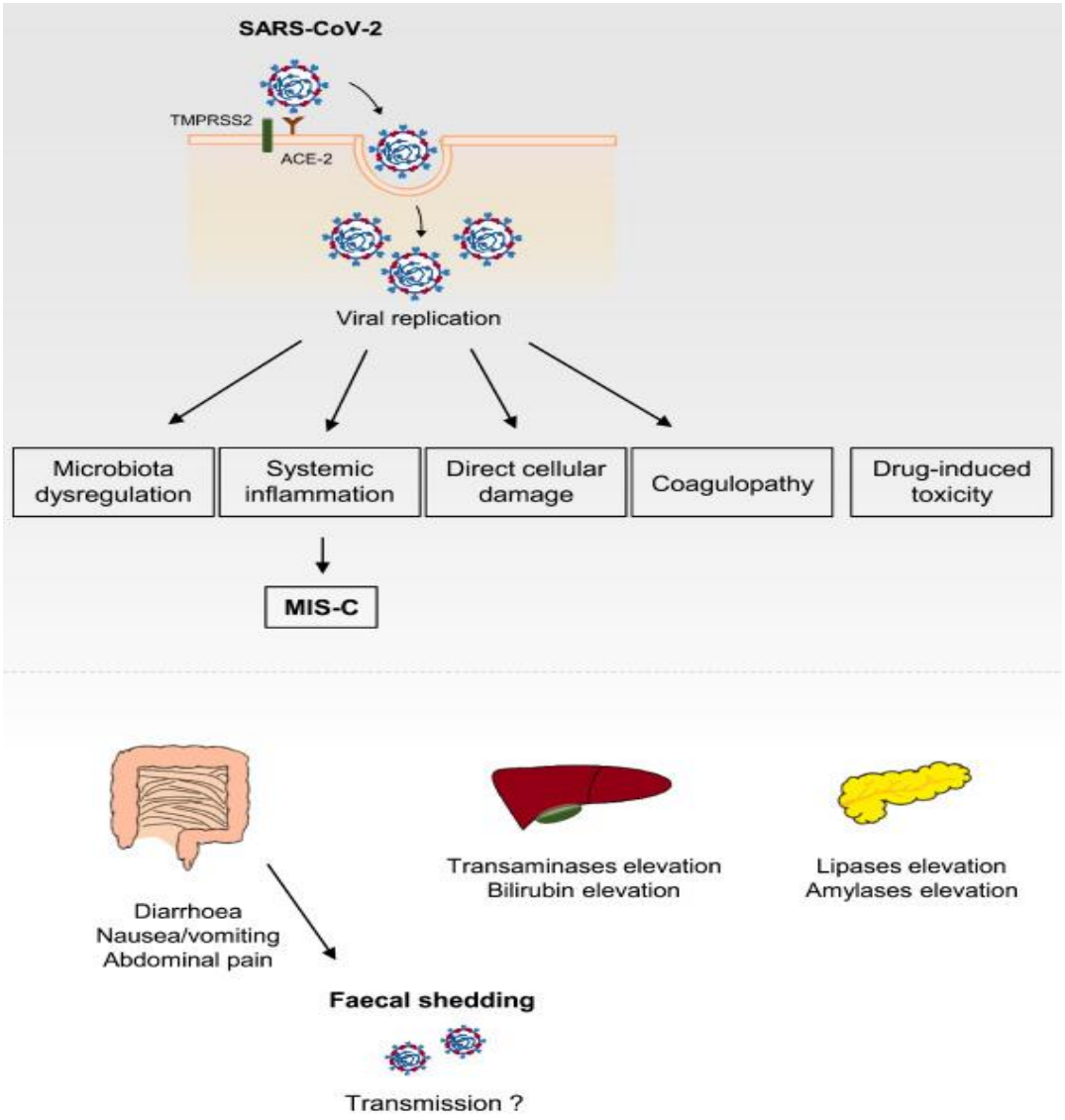
FIGURE 2. Pathophysiological processes that may lead of liver injury in COVID-19. Following SARS-CoV-2 infection, liver injury may result due to direct cytopathic effects (due to viral entry through ACE2 receptors on hepatocytes and cholangiocytes) or hypoxia-induced damage (resulting from ARDS or pneumonia-associated hypoxia) or bacterial translocation and inflammation (direct viral injury and ischemic injury of the gut or disruption of gut–mucosal barrier) or systemic hypotension and cellular ischemia, abnormal coagulation/microthrombi, endothelial dysfunction (resulting from exaggerated immune responses/systemic inflammation) or cardiac congestion from right heart failure (due to myocardial dysfunction), or drug-induced liver injury or exacerbation of chronic liver disease. SARS-CoV-2 = severe acute respiratory syndrome corona virus 2; ACE2 = angiotensin-converting enzyme 2; ARDS = acute respiratory distress syndrome; CLCD = chronic liver cell disease. This figure appears in color at www.ajtmh.org.

The major pathophysiological features of liver injury include:

- Enlargement of liver volume,
- Liver cell focal necrosis with neutrophil infiltration,
- Hepatocyte steatosis,
- Lobular and portal inflammation, hepatic sinus congestion,
- Microthrombosis , and high filling of the gallbladder.
- These pathological changes in the liver suggested that the degree of liver injury in most COVID-19 patients was **mild**

	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Incidence of liver injury	60%[6]	60%[6]	14.8–53%[8]
Expression of entry receptor on cholangiocytes	NA	NA	ACE2 receptor expression is higher than on hepatocytes[9]
Expression of entry receptor on hepatocytes	ACE2 receptor expression is abundant[9]	DPP-4 receptor expression is high in liver[10]	ACE2 receptor expression is low[9]
Expression of entry receptor in Kupffer cells, liver endothelial cells, and other inflammatory cells	NA	NA	ACE2 receptor is expressed[9]
Liver enzyme level	Mild to moderate elevation of ALT and AST—53%[11]	Elevation of ALT and/or AST[12,13]	Elevation of ALT 23.3% and AST 23.4%[14]
Albumin level	Decreased serum albumin[1]	Decreased levels of albumin[12,13,15]	Decreased levels of albumin 61.3%[14]
Bilirubin level	Increased serum bilirubin[6]	Increased serum bilirubin[12,13]	Increased serum bilirubin 27.9%[4]
Serum GGT level	NA	NA	Increased in severe cases 27.9%[14]
Pathological manifestations of liver injury	Antemortem Mild lobular activities with occasional acidophilic bodies and prominent Kupffer cell Mildly inflamed portal tracts with lymphocytic infiltration Nonspecific inflammation in the liver in biopsy Hydropic degeneration Steatosis Focal necrosis[6] Postmortem histopathological findings- Necrosis Nodular cirrhosis Minor inflammatory changes Hydropic and fatty degeneration Interstitial cell proliferation	Postmortem histopathological findings Mild chronic lymphocytic portal and lobular inflammation Reactive parenchyma with mild cellular hydropic degeneration Rare multinucleated hepatocytes and mild disarray of the hepatic plates Mild sinusoidal lymphocytosis and small necroinflammatory foci in the hepatic lobules Congestion, hemorrhage, and focal perivenular loss of hepatocytes Macrovesicular perivenular	Postmortem histopathological findings Microvescicular steatosis Mild lobular and portal activity[16] Hepatomegaly Hepatocyte degeneration Lobular focal necrosis Neutrophil infiltration (lymphocytes and monocytes in portal area) Congestion of hepatic sinuses with microthrombosis Mild sinusoidal dilatation Mild lobular lymphocytic infiltration Patchy hepatic necrosis in the periportal and centrilobular areas

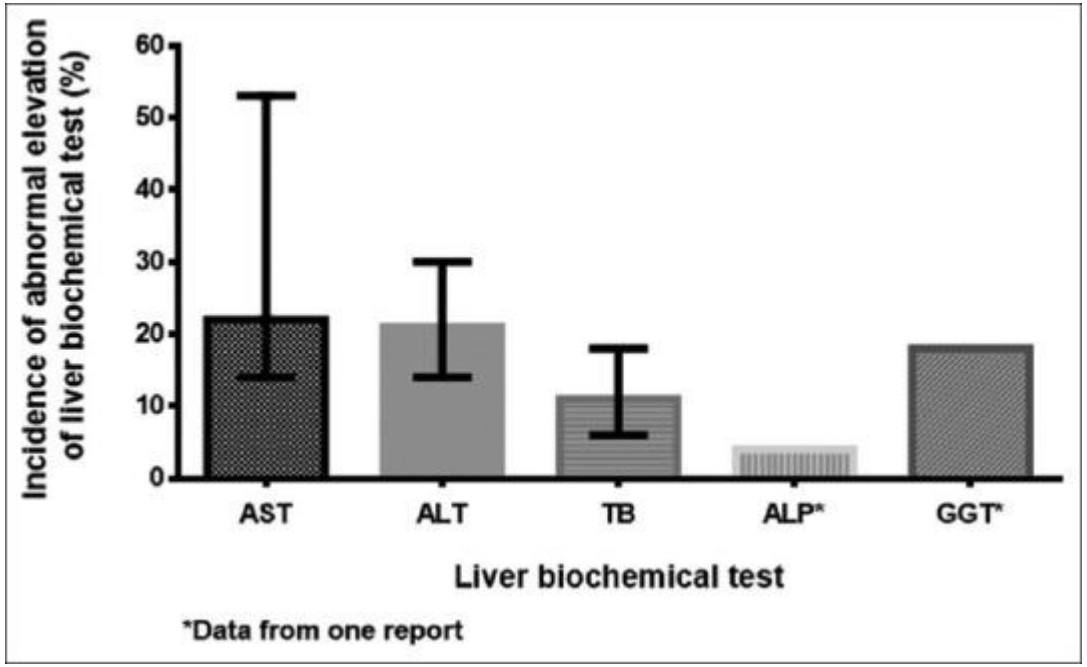
- Reactivation of pre-existing liver disease: patients with pre-existing chronic liver disease, may be more susceptible to liver damage from SARS-CoV-2.
- Biological drugs like tocilizumab and baricitinib might also cause HBV reactivation and thus lead to liver function deterioration.
- On the other hand, it is still unknown whether SARS-CoV-2 infection exacerbates cholestasis in those with underlying cholestatic liver disease.


SARS-CoV-2
TMPRSS2
ACE-2
Viral replication
Microbiota dysregulation
Systemic inflammation
Direct cellular damage
Coagulopathy
Drug-induced toxicity
MIS-C
Diarrhoea
Nausea/vomiting
Abdominal pain
Transaminases elevation
Bilirubin elevation
Lipases elevation
Amylases elevation
Faecal shedding
Transmission ?

ADULTS	CHILDREN vs ADULTS
SARS-CoV-2 infection *via* ACE2 in the GI tract, liver, and pancreas	
Few data on histology abnormalities	GI symptoms before or without respiratory symptoms
Diverse microbiota alterations described in SARS-CoV-2 infection	GI involvement is typical of MIS-C
GI symptoms in around 20% of patients (i.e., anorexia, nausea, vomiting, diarrhea, and abdominal pain)	Putative prolonged faecal shedding in children
COVID-19 severity associated with GI symptoms	Children with IBD on immunosuppressive regimens do not have an increased risk of severe COVID-19
IBD patients not at increased risk of SARS-CoV-2 infection	
Different patterns of COVID-19 associated liver damage (*i.e.*, direct viral infection, medications, chronic hypoxia)	Mild to moderate liver involvement in children
Transaminase elevation in between 14 and 53%	Unclear incidence of cholestasis in children
Transaminase elevation associated to GI symptoms	High ALT and low albumin in MIS-C
Unclear association of transaminase elevation with severe COVID-19, ICU admission, and mortality	Children with CLD do not have an increased risk for severe disease course
CLD (cirrhosis) associated to increased mortality of COVID-19	
Pancreatic enzymes laboratory abnormalities in 10% of adults with COVID-19	Unknown rate of pancreatic enzyme abnormalities in children
Overt pancreatitis rarely reported	Anecdotic descriptions of SARS-CoV-2 associated pancreatitis
Pancreatic damage in patients with severe disease	

A

B


Incidence of abnormal elevation of liver biochemical test (%)
60
50
40
30
20
10
0
AST
ALT
TB
ALP*
GGT*
Liver biochemical test
*Data from one report

- In children, as in adults, most patients have mild-to-moderate ALI (transaminases <2 to 2–5 times the upper limit of normal), and the severity of liver involvement parallels the seriousness of SARS-CoV2 infection in general
- More severe liver injury, characterized as transaminases >5 times the upper limit of normal, is seen in the setting of shock, hypoxia/respiratory compromise, longer overall hospital length of stay, and higher serum inflammatory markers.
- Multisystem Inflammatory Syndrome in Children
- MIS-C (or PIMS-TS, Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV2) is a rare but severe late complication described in children associated with previous or ongoing SARS-CoV2 infection. Unlike severe pediatric COVID-19, the syndrome mainly affects children without comorbidities

- In a multicenter cohort study by Lavarone et al., the mortality of those with cirrhosis was significantly higher than those without cirrhosis (34% versus 18%,respectively).
- Another study by Marjot et al. in autoimmune hepatitis patients found that autoimmune hepatitis (AIH) and immunosuppression were not significantly associated with death despite the use of medications that suppressed the immune system
- Furthermore, a strong correlation between the stage of liver disease and the rate of intensive care unit (ICU) admissions, renal replacement therapy, and death was found. The cause of death in patients with CLD/cirrhosis was respiratory related in the majority (71%) and 19% were liver related.
- Furthermore, baseline liver disease stage and alcohol-related liver disease were risk factors for death from COVD-19.
- Further, the mortality associated with cirrhosis was higher than among those with cirrhosis and bacterial infection.

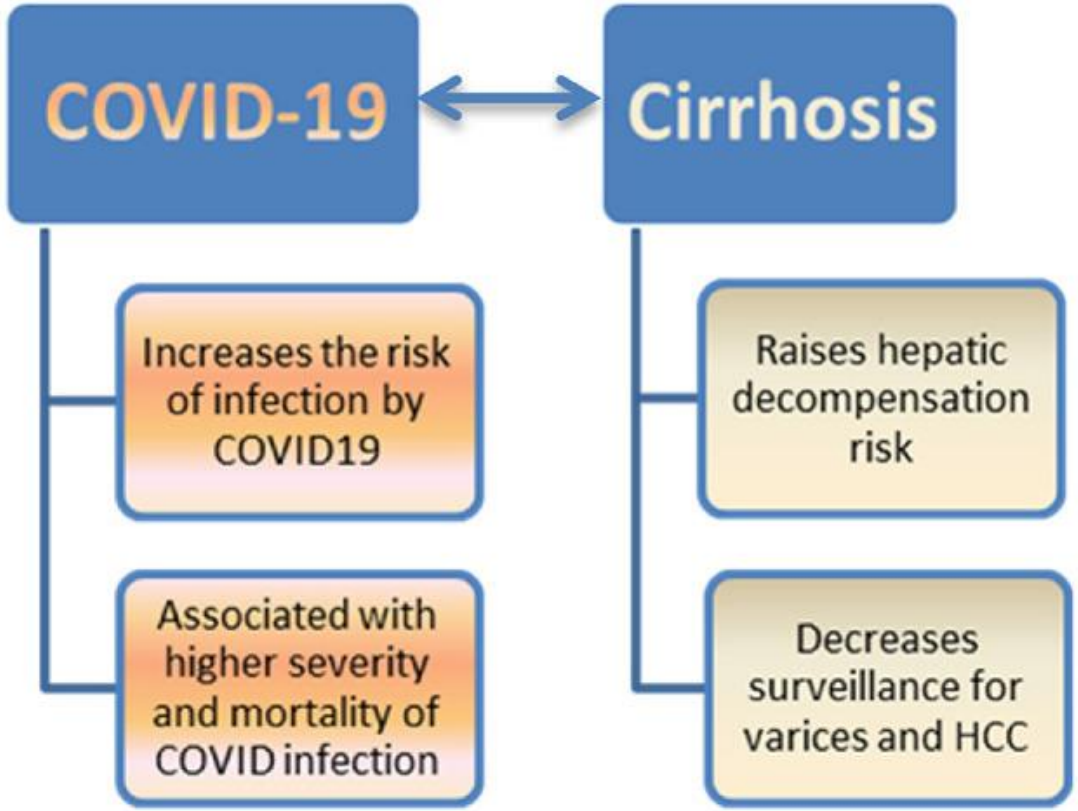
Questions and answers

- Obesity (severe Covid)
- NAFLD(severe Covid)
- Children diagnosed with MIS-C can have acute liver injury with elevated liver enzymes that is most commonly self-limited, though ALF has also been reported
- End stage liver disease (Decompensation)
- *ALF in SARS-CoV2 infection is rare.*

- *No reduction or withdrawal of immunosuppressive drugs*
- SARS-CoV2 vaccination should be recommended for all children 12–17years of age with chronic liver disease, including autoimmune liver disease on immunosuppressive therapies, patients with cirrhosis, transplant recipients, those on the waiting list for LT and their caregivers.
- The diagnostic approach and the general management strategies of children with SARS-CoV2 infection do not differ between those with and without CLD or in those who have undergone LT

- A decompensation is described following SARS-CoV-2 infection in adults with chronic liver disease (CLD), particularly in those with associated obesity or diabetes . When liver damage is documented, in both MIS-C and severe COVID-19, vascular thrombotic events should be taken into consideration

- Key points
- Abnormal liver biochemical test can be found in up to 53% of patients with COVID-19 infection
- Mildly elevated AST or ALT is the most common presentation
- Although not proven in SARS-CoV-2, SARS-CoV-1 directly caused liver damage
- Outcome data is needed for patients with underlying chronic liver disease or patients who have a received liver transplantation.


COVID-19
Cirrhosis
Increases the risk of infection by COVID19
Associated with higher severity and mortality of COVID infection
Raises hepatic decompensation risk
Decreases surveillance for varices and HCC