



## RESEARCH ARTICLE - MEDICAL TECHNIQUES

# Liver damage during infections with coronavirus

Iqbal Hanash Dhefer<sup>1\*</sup>

<sup>1</sup> Department of Nursing, AL-Suwaira Technical Institute, Middle Technical University, Iraq.

\* Corresponding author E-mail: [driqbalhanasd@gmail.com](mailto:driqbalhanasd@gmail.com)

Article Info.	Abstract
<p><i>Article history:</i></p> <p>Received 02 March 2021</p> <p>Accepted 29 June 2021</p> <p>Publishing 30 June 2021</p>	<p>The pathogen of the new 2019 coronavirus disease (COVID-19), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presented a significant risk to health care. The WHO has described the SARS-CoV-2 infection outbreak as an international public health emergency. The main damage caused by the infection with SARS-CoV-2 was known to be lung infections. Previous research revealed that liver damage is prevalent in patients infected with the additional widely zoonotic coronaviruses, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), and has been reviewed in relation to the severity of MERS, SARS, and COVID-19 diseases. Likewise, the mechanism and features of liver damage and liver injury has also been observed, as outlined in this review, which results in extreme cases during the phases of the disease.</p>
<p><b>Keywords:</b> Liver; COVID; damage; SARS; injury</p>	

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## 1. Introduction

Coronavirus2 (SARS\_COV\_2) is a new pathogenic coronavirus known as COVID-19 that causes severe respiratory disease in humans [1]. COVID-19 is a public epidemic issue not just due to accelerated horizontal exposure, but due to the public infrastructure and economic consequences [2].

The results show that different degrees of liver damage can occur in patients infected with SARS-COV-2 and SARS-CoV. In COVID-19 patients, the irregular liver malfunction of liver disorder may be observed, whether in the type of cholestasis, hepatitis, or even both [3]. Serum alanine aminotransferase (ALT) elevation was observed in 28 % of 99 COVID-19 cases, and elevated total bilirubin was documented in 18% of the same patients in an early study in China [4]. With the severity of COVID-19, the effectiveness of liver dysfunction will increase. Liver function tests are standard or slightly raised for early SARS-CoV-2 infection. In liver histology showed moderate lobular, syncytial multinuclear hepatocytes and portal function micro vascular steatosis [5]. Electron microscopy showed endoplasmic reticulum dilatation, mitochondrial swelling, damaged cell membranes, and glycogen depletion. Electron microscopy is used to display endoplasmic reticulum dilatation, mitochondrial swelling, weakened cell membranes, and glycogen depletion [6]. Data indicates that within hepatocytes, SARS-CoV-2 also replicates [7]. The slight rise in aminotransferases and the lack of apparent necrosis suggest a mild liver damage caused by SARS-CoV-2[8].

The required cell entry ACE2 receptor expressed by hepatocytes and cholangiocytes [8]. While extreme liver damage documented in patients with acute COVID-19, several reasons such as hypoxemic, sepsis-associated cholestasis, drug-induced liver injury, and hypotensive ischemic hepatitis are likely to trigger it. Various of the medications utilized in serious situations of liver damage, like those used to prevent infection of SARS-CoV-2, including lopinavir, ritonavir, and remdesivir, have been associated with hepatotoxicity. This faster review will discuss the mechanisms and liver damage features produced by SARS-CoV-2 and SARS-CoV infections that can provide information for further research on liver damage done by COVID-19.

<b>Nomenclature</b>			
COVID-19	coronavirus disease 2019	SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome	GGT	gamma glutamyltransferase
ALT	alanine aminotransferase	AST	aspartate aminotransferase
CLD	chronic liver disease	ARDS	acute respiratory distress syndrome
NAFLD	nonalcoholic fatty liver disease	ICU	intensive care unit

## 2. Medical Characteristics

Early investigations from China indicated that the infection rate for SARS-CoV-2 was three to seven days and sometimes two weeks, respectively. The maximum infection rate reported was 12.5 days [9]. Whilst the most important clinical characteristics of COVID-19 from a Chinese resident studies reported fever (>38C), fatigue, dry cough, leukopenia, myalgia and elevated liver enzymes. Vomiting, diarrhea, and nausea were realized in 2% to 10% of COVID-19 patients. In Wuhan's recent case series by Wang and coworkers [10], 138 hospitalized patients with COVID-19; 54.3% were males and average age was 56 years (22–92 years). Clinical characteristic was dry cough 59.4%, fever 98.6%, lymphopenia (70.3%), fatigue 69.6%, raised lactate dehydrogenase (LDH) 39.9%, and prolonged prothrombin time 58%. In the intensive care unit (ICU) 63 patients (26.1%) were treated for shock (30.6%), acute respiratory distress syndrome (61.1%), and cardiac arrhythmias (44.4%). Intensive care patients needing were senior (66 vs. 51) and more frequently had chronic diseases (72% vs.32%). Aspartate aminotransferase (52 vs. 29) , lactate dehydrogenase LDH in (435 vs. 212), and hypersensitive cardiac troponin in (11 vs. 5.1) were greater in patients sent to the ICU. The thoracic scan revealed bilateral pneumonia in all 138 cases. The study of non-survivors and survivors found a greater white blood cell count in the non-survivors with extreme advanced lymphopenia. With the progression of the disease, these patients requested organ care for the gradual renal dysfunction prior to death. Throughout the highest database study by Guan and coworkers for 1,099 patients from China with COVID-19 reported, 58 % were male and 23, the average age for diagnosis was 47 years (35-58). Most main presenting symptoms were cough (67.8%), diarrhea (3.8%), fever (88.7%) and nausea or vomiting (5%). CT chest radiography showed bilateral patchy shadows (51.8%) and ground glass opacity (56.4%). Of 1,099 patients, 2.3% suffered invasive ventilation, 5% were sent to the ICU and 1.4% died [11].

## 3. The COVID-19 and Liver Damage

COVID-19 can lead to aggravation of un treated chronic liver disease, guiding to hepatic decomposition, higher death rate, and liver failure. Table 1 offers a list of newly available research. Generally, 2 to 11 percent amongst COVID-19 cases were recognized to have liver disease, especially individuals with extreme COVID-19[12]. These data are from bolt data during the early pandemic from China and some of the data at the US, Zang et al. analyzed the effects of the virus on the liver and found 14% to 53 % involvement of patients have normal AST and ALT [13]. Acute liver injury was found in 1.5 % of the 5700 hospitalized patients in new york and chronic liver failure cases were observed in a recently approved new york study by Safiya Z et al. Other bolt data from China studies showed that the abnormal liver test was detected in between 12% to 78% of their patients [14]. In China's latest study, 23 patients (2.1%) appeared active for HBsAg, and only one that had chronic COVID-19[15]. Another Wuhan study conducted by Wang and associates, found that four patients with COVID-19(2.9%) had ongoing liver problems [16]. Interestingly, a comparative study found that only 4% had ongoing chronic Hepatitis-B between 161 survivors and 113 non survivors [17]. In another study Xu and coworkers, from outside Wuhan recognized 26 COVID-19 patients of which 2.9 % got liver disease [18]. Thirteen of the 274 patients with acute liver damage were observed and 10 of them had died [17]. The existing data clearly show that increased liver enzymes are mainly found in patients with critical cases with COVID-19. 274 patients with acute liver injury, [13] were diagnosed and 10 died [17]. In 8 (62 %) out of 13 patients in ICU, increased AST was observed compared to 7(25 %) out of 28 in the outside of the ICU [19]. In extreme COVID-199, the peak AST (1,445 U/L) and ALT (7,590 U/L) levels observed [20]. Intriguingly, elevated the enzyme ratio was found in subjects undergoing upkeep with ritonavir/lopinavir (25% vs. 2556.1 %) [21]. Surprisingly, more patients developed elevated transaminases in spite of the existence of ACE2 in cholangiocytes [22]. Data collected from Xu et al. in Wuhan, China presented elevated levels of gamma glutamyltransferase in extreme subjects of COVID-19[23]. The elevation of liver enzymes in this population is unknown, whether it caused by the disease itself or from liver injury due to medication. In extreme COVID-19 cases, potential liver damage caused by overflowing cytokine production [22]. Hepatic malfunction is probable to occur from cytokine overflowing instead the directly cytopathic virus influences. Further information wanted to determine the trend and grade of liver damage in COVID-19 cases.

### 3.1. Pathophysiology of Liver Infection

The study by Xu, et al reported the death of the patient infected with COVID-19 because of mild microvascular steatosis and inflammation in the portal tract and hepatic lobes located in the liver histology. At this point, although it is uncertain if these effects are due to the virus-related infection or medications. In particular, peripheral blood testing presented substantially diminished but proinflammatory hypersensitive CD8 and CD4 cells, with elevated Th17, CCR6+, CD4 and T cells with granulations of cytotoxic effect in CD8 cells, that might furthermore lead to hepatocyte failure [24]. In alternative paper liver surgeries demonstrated after death in four COVID-19 cases focal macrovesicular steatosis and moderate sinusoidal dilatation. Moderate lobular lymphocytic invasion occurred in portal areas that was not important. In one of the patients, RNA of SARS-CoV-2 was separated via RT-PCR from tissue of liver [25].

In spite of higher ACE2 levels receptors' that expressed by the bile duct epithelium, but there wasn't really any evidence that points to injure to the bile duct[25], but it could be due to direct damage of the hepatocytes and cholangiocytes as both of them have the ACE2 receptor the target of virus , so that all patients with COVID whither severe or mild were not showed the abnormal liver test or liver damage .The second

mechanism could be related to translocation from the virus from the intestine to the portal blood and subsequently to the liver that will evidence as 2% to 10% of patients can present with diarrhea and the virus was found in the stool of the affected patients.

The third mechanism is drug hepatotoxicity remembered those patients were on multiple medication seems there is no current treatment for that includes antibiotic, antimalarial, remdesivir, and all of these medications could cause to the abnormal liver testing that observational study by Zhang and his coworkers showed AST/ALT increase even after control of infection .Lastly, and the most important the immune mediated inflammation evidenced by the cytokine storm that is particularly found during sever the disease.

Table 1 Liver related studies

Study	Design	Finding
Zhang Y, et al.[26]	N=115 COVID patients N=119 community-acquired pneumonia patients retrospective	No difference AST,ALT elevation between groups. Albumin lower in COVID group
Bangash MN, et al.[27]	Correspondence –review of 7 studies	AST,ALT 1-2xULN most severe COVID cases ,AST,ALT2xULN. Elevation in CK 0 decompensated cirrhosis had COVID symptoms at authors' hospital vs 17% decompensated cirrhotic at other Wuhan hospitals
XiaoY, et al.[28]	111 Decompensated cirrhosis enrolled in prevention study	Recovered, received oseltamivir and antivirals
Qin J, et al.[29]	Case report 37 years old man OLT for HBV,HCC	No significant COVID disease among, 200 LT recipients, 100 AIH patients, 3 recipients test positive
D'Antiga , et al.[30]	Bergamo-Peds , Transplant center experience	Presents an algorithm for dedicated transplant pathway
Andrea, et al.[31]	Milan-transplant center experience	unusual AST 58.06%, ALT 13.33% and TB 12.90% . All patients were died .
Huang , et al.[32]	36 COVID-19 patients	Greater ALT and AST in patients who deceased. large mortality (76.9%)in patients with acute liver damage.
Chen et al.[33]	99 COVID-19 patients	Moderate rise of ALT and AST. The underlying CLD was 3.9% in patients with COVID-19. 4.3 % mortality .
Wang, et al. [10]	138 patients with the COVID-19	Unusual ALT (21.3 %), AST (22.2 %) and TB (10.5 %). Chronic hepatitis B infection occurred in 2.1 % of patients with COVID-19. 1.4 % death . 1 (4%) of COVID-19 patients had underlying CLD.
Guan, et al.[15]	N=1099 COVID patients	A larger percentage of liver injury patients (56.1%) got treatment with ritonavir/lopinavir relative to those without liver damage(25 %)respectively.
Fan , et al.[21]	148 COVID-19 patients	Unusual AST and ALT 53%. 3% had underlying CLD.
Lu, et al. [34]	52 COVID-19 patients	7 of COVID-19 patients(3%) had underlying CLD. In patients with ARDS-related deaths, bilirubin was substantially higher.
Shi, et al.[35]	N=81 COVID patients	In patients with serious illness, greater GGT, AST and ALT and. The NAFLD patients had serious illnesses. The liver damage rate in serious cases (36.2 % ) was notably greater than that of moderate cases (9.6 %).
Cai, et al. [36]	N=298 COVID patients	7% had underlying CLD in COVID-19 patients .
Li, et al. [37]		Unusual AST and ALT in severe patients only
Cao, et al.[38]	N=128 COVID patients	No variation in frequency of liver damage between non-survivors (28 % ) and survivors (30 % ) and
Yang, et al.[39]	52 COVID-19 patients	

#### 4. SARS and Liver Damage

An infectious disease induced by SARS-CoV is severe acute respiratory syndrome (SARS)[40], which was first detected in November 2002 in the Chinese city of Guangdong and Hong Kong and has spread rapidly to 29 cities around the world. About 10% of patients suffer from CLD, especially chronic hepatitis B, possibly because of the SARS outbreak's geographical position. More than 50 percent of patients developed (mainly moderate) irregular liver function tests and the others improved. In various studies, increased liver function tests, an expected elevation ALT in the ICU and mortality in general were related with severe diseases, this elevated the probability of SARS affected liver dysfunction instead of just being related with it [40-47].

A variety of studies observed that SARS patients suffer liver damage and a slight to mild increase of AST or ALT levels, or both, in the early stages of infection. Most patients had reduced levels of serum albumin and raised levels of serum bilirubin [48-58]. Also, Numerous studies conducted to identify the mechanism of liver damage due to SARS-CoV [59-61]. In SARS patients massive numbers of virus particles found in parenchymal cells, and vascular endothelium of the liver, and SARS was known to use angiotensin-converting enzyme 2 (ACE2) as receptor to enter the cell, which is broadly expressed in endothelial cells of the liver, making the liver a potential target for SARS-CoV [59-63].

Liver biopsies showed a substantial elevated in eosinophilia bodies with balloon-like hepatocytes, and mitotic cells in cases with SARS, proposing that SARS may stimulate apoptosis of cells the liver and therefore initiate the liver damage [6].

Several different papers presented that during the caspase-dependent pathway, SARS-CoV-specific protein 7a be able to stimulate cell lines apoptosis of various organs like the kidney, lung and liver, targeting tissue of the liver and causing liver damage [64]. In SARS-CoV patients with early infection, abnormal serum levels of chemokine's and cytokines have been observed. Duan et al revealed that in cases with abnormal liver function, serum levels of IL-6, IL-10, and IL-1 were greater than in normal liver function cases, indicating a potential related between liver damage and SARS-CoV infection- stimulated inflammatory responses [45]. Additionally, due to the increased proliferation of the hepatitis virus through infection with SARS, the patients with SARS that infected with hepatitis B / HCV virus were further susceptible to liver damage and acute hepatitis, as well as steroids, quinolones, macrolides, ribavirin and other medication utilized for patients of SARS, it can also damage the liver[43,46,49].

#### 5. MERS and Liver Damage

The first infection with the MERS' virus was identified in Saudi Arabia in 2012 [65], and low albumin levels were considered a distinct indicator of extreme MERS disease [66]. In MERS patients, liver biopsy indicated moderate hydropic hepatocyte degeneration and lobular lymphocytic infiltration [67,68]. In recovering MERS patients, had fewer liver injuries than in non-recovering patients (77.9% versus 91.3%), and mortality was higher in patients with comorbidities [69,70].

#### 6. Conclusion

Liver damage mechanisms that happened throughout infection with SARS-CoV-2 remains obscure. Our limited knowledge indicates that generally pathogenic human coronavirus infection can cause liver damage due to immunopathology caused by excessive inflammatory response and/or direct cytopathic pathogen effects.

In the meantime, in patients with viral hepatitis, SARS-CoV may exacerbate liver damage, despite the lack of reason yet for SARS-CoV-2 and MERS. Clearly, medication stimulated liver damage must not be neglected when treating of coronavirus infection and must be carefully examined. In addition to the active treatment of the primary infection caused by coronavirus disease, from a therapeutic point of view, consideration must also be given to controlling the incidence of liver damage and the use of medicines that may trigger liver damage, including steroids or quinolone antibiotics, macrolide, etc. It is advisable to treat patients with liver damage with drugs that could both inhibit inflammatory responses and protect liver functions. Extreme acute liver injury cases with a higher mortality rate have been recorded. To characterize the degree and trigger of liver damage in COVID-19, future research with deep actually follow are necessary. Detailed evaluation is expected of the influences of COVID-19 on chronic liver disease, with further investigation needed in this field.

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