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# Liver injury during highly pathogenic human coronavirus infections

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**Abbreviations:**

SARS-Cov-2, severe acute respiratory syndrome coronavirus 2

COVID-19, 2019 novel coronavirus disease

WHO, the World Health Organization

SARS-CoV, severe acute respiratory syndrome coronavirus

MERS-CoV, the Middle East respiratory syndrome coronavirus

SARS, severe acute respiratory syndrome

MERS, the Middle East respiratory syndrome

CoVs, coronavirus

HCoV-NL63, human coronavirus NL63

HCoV-229E, human coronavirus 229E

HCoV-OC43, human coronavirus OC43

HCoV-HKU1, human coronavirus HKU1

ARDS, acute respiratory distress syndrome

MOF, multiple organ failure

ALT, alanine transaminase

AST, aspartate aminotransferase

RT-PCR, reverse transcription-polymerase chain reaction

ACE2, angiotensin converting enzyme II

IL-1, interleukin- 1

IL-6, interleukin- 6

IL-10, interleukin- 10

HBV, hepatitis B virus

HCV, hepatitis C virus

DPP-4, dipeptidyl peptidase -4

hDPP-4,human dipeptidyl peptidase -4

IFN, interferon

TNF, tumor necrosis factor

IL15, interleukin- 15

IL17, interleukin- 17

ALB, albumin

TB, total bilirubin

GGT, gamma-glutamyl transferase

AKP, alkaline phosphatase

ALB, albumin

## Conflict of interest

The authors disclose no conflicts of interest.

## Author contributions

Xin Zheng designed and planned the work, and revised the manuscript. Ling Xu and Jia Liu performed the literature search and interpretation, and manuscript drafting. Mengji Lu and Dongliang Yang revised the manuscript.

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**Abstract**

The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), the pathogen of 2019 novel coronavirus disease (COVID-19), has posed a serious threat to global public health. The WHO has declared the outbreak of SARS-CoV-2 infection an international public health emergency. Lung lesions have been considered as the major damage caused by SARS-CoV-2 infection. However, liver injury has also been reported to occur during the course of the disease in severe cases. Similarly, previous studies have shown that liver damage was common in the patients infected by the other two highly pathogenic coronavirus - severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), and associated with the severity of diseases. In this review, the characteristics and mechanism of liver injury caused by SARS-CoV, MERS-CoV, as well as SARS-CoV-2 infection were summarized, which may provide help for further studies on the liver injury of COVID-19.

**Key words:** Liver Injury, SARS, MERS, SARS-CoV-2，COVID-19

**Key points**

- Reports of liver injury during SARS-CoV, MERS-CoV and SARS-CoV-2 are summarized.
- Possible mechanisms of coronavirus infection-induced liver injury are introduced and

## Introduction

Coronavirus (CoVs) is a virus of the coronavirus family, which has the largest genome of all known RNA viruses and is widely found in humans, mice, pigs, cats, dogs and other animals. Seven coronavirus species are known to cause human disease, of which four species (HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1) cause respiratory infections in immunocompromised individuals, infants, and the elderly [1]. The other three are highly pathogenic human coronaviruses, including the severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV) and the 2019 new coronavirus (SARS-CoV-2) (summarized in Table 1). These three viruses can cause respiratory, intestinal, hepatic and neuronal diseases, and may lead to acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death in severe cases [2-4]. Studies have shown that patients infected with SARS-CoV, MERS-CoV, and SARS-CoV-2 may develop different degrees of liver injury. In this review，the characteristics and mechanism of liver injury caused by SARS-CoV, MERS-CoV, as well as

SARS-CoV-2 infection were summarized, which may provide help for further studies on the liver injury of COVID-19.

## 1. SARS-CoV and liver injury

Severe acute respiratory syndrome (SARS) is an acute infectious disease caused by SARS-CoV [5]. It was first reported in Guangdong Province and Hong Kong of China in November 2002, and soon spread to 29 countries and regions around the world. Patients with SARS-CoV infection are characterized by persistent fever, headache, muscle pain and decreased white blood cell count. Severe cases may develop ARDS and MOF [2]. A number of studies have shown that liver injury occurred in SARS patients, which was mainly manifested in the mild and moderate elevation of ALT and/or AST during the early stage of the disease. Some patients had decreased serum albumin and increased serum bilirubin levels [6-18]. The severe cases were more likely to have severer liver injury compared to mild cases [6, 10, 12].

Studies have been performed to understand the mechanism of liver damage caused by SARS-CoV. Autopsy of SARS patients found large numbers of virus particles not only in the lungs but also in the parenchymal cells and vascular endothelium of other organs, including the liver[19, 20]. SARS-CoV genome was also detected in hepatocytes by RT-PCR [19, 20]. It is known that SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) as the receptor for cell

entry [22]. ACE2 was found to be abundantly expressed on endothelial cells of the liver [23], which makes the liver a potential target for SARS-CoV. Liver biopsies in SARS patients showed a significant increase in mitotic cells, with eosinophilic bodies and balloon-like hepatocytes, suggesting that SARS-CoV may induce apoptosis of liver cells and thus cause liver injury [18]. Other studies showed that SARS-CoV-specific protein 7a can induce apoptosis in cell lines of different organs (including the lung, kidney and liver) through the caspase-dependent pathway, further confirming the possibility that SARS-CoV directly attacks liver tissue and causes liver injury [24].

Abnormal serum levels of cytokines and chemokines were found at the early stage of SARS-CoV infection in patients. Duan et al.[12] reported that serum IL-1, IL -6 and IL -10 levels in patients with abnormal liver function were higher than those in patients with normal liver function, suggesting a possible correlation between liver damage and the inflammatory responses induced by SARS-CoV infection. Besides, SARS patients with HBV/HCV infection were more prone to develop liver damage and severe hepatitis, which is probably due to enhanced replication of hepatitis virus during SARS-CoV infection [13]. It is particularly worth noting that antibiotics (macrolides, quinolones), antivirals (ribavirin), steroids and other drugs used for the treatment of SARS patients may also result in liver damage [7, 25].

## 2. MERS-CoV and liver injury

Most Middle East respiratory syndrome (MERS) cases, caused by MERS-CoV infection, were firstly occurred in Saudi Arabia in 2012. The virus has since spread to Europe, Asia, Africa and North America [3]. MERS-CoV infection in patients is characterized by fever, cough, and shortness of breath. Severe MERS patients quickly progressed to respiratory and kidney failure [26]. Besides, a number of retrospective studies have shown that patients with MERS had elevated liver enzymes and bilirubin levels, as well as decreased albumin levels [27-32]. It has also been shown by Saad et al. that the intensity of the albumin level decrease was a predictor of disease severity [27]. Similar to the observation in SARS patients, the pathological manifestations of liver injury in MERS patients are mild portal tract and lobular lymphocytic inflammation, as well as mild cellular hydropic degeneration in hepatic parenchyma [33, 34].

Different from SARS-CoV, MERS-CoV was found to utilize dipeptidyl peptidase -4 (DPP-4) as its functional receptor for establishing infection in cells [35]. The expression level of DPP-4 in the liver is high [36], suggesting it is a potential target organ of MERS-CoV. Zhao et al. [37] constructed a transgenic mouse model globally expressing codon-optimized human DPP-4 (hDPP-4) and found that MERS-CoV is able to infect the liver cells via DPP-4 on the cell surface and cause cell damage. Mild to moderate liver injury occurred on day 5 after MERS-CoV infection in the hDPP-4 transgenic mice, and the main findings were scattered necrosis of liver cells in the hepatic sinus, infiltration of large numbers of activated Kupffer

cells and macrophages. Fatty changes in liver cells were observed on day 9 post-infection with less liver cell necrosis [37].

Significant pro-inflammatory cytokine responses were observed in the acute phase of MERS-CoV infection in patients, and the concentrations of serum IFN-γ, TNF-α, IL-15，and IL-17 were significantly increased [38]. However, studies on the correlation between pro-inflammatory cytokine responses and liver injury are still lacking. It remains to be explored whether the liver injury observed during MERS-CoV infection is the consequence of direct viral infection, inflammation-mediated pathogenesis, or applicating liver-damaging drugs during the course of treatment.

## 3. SARS-CoV-2 and liver injury

COVID-19 is a novel infectious disease caused by SARS-CoV-2. In December 2019, pneumonia cases of unknown origins were firstly identified in Wuhan City, Hubei Province, China, and then rapidly spread to the whole country, and up to date, more than 70 countries worldwide. Currently, the number of SARS-CoV-2 infected patients is still rapidly increasing on a global scale [39]. Mild cases of COVID-19 showed symptoms of fever, fatigue, dry cough, vomit, and diarrhea. In severe cases, respiratory distress and/or hypoxemia occurred one week after the onset of the disease and then deteriorated into ARDS, septic shock, metabolic acidosis, and even death [40].

Recent studies on COVID-19 have shown that the incidence of liver injury ranged from 14.8%-53%, mainly indicated by abnormal ALT/AST levels accompanied by slightly elevated bilirubin levels [40-51]. The albumin is decreased in severe cases and the level of albumin is around 26.3-30.9 g/L [46]. The proportion of developing liver injury in severe COVID-19 patients was significantly higher than that in mild patients [40-42]. In death cases of COVID-19, the incidence of liver injury might reach as high as 58.06% [51] and 78% [50]. One study reported that serum ALT and AST levels increased up to 7590 U/L and 1445 U/L respectively in a severe COVID-19 patient [46]. Our unpublished data showed very similar findings to other studies, except that we found that serum GGT increased in severe cases and serum AKP level was at normal range in both mild and severe cases. Currently, studies on the mechanisms of SARS-CoV-2 related liver injury are limited. It has been shown that SARS-CoV-2 also uses ACE2 as its entry receptor as SARS-Cov does [52]. Chai et al. [53] found that both liver cells and bile duct cells express ACE2. However, the ACE2 expression of bile duct cells is much higher than that of liver cells, but to a comparable level of alveolar type 2 cells in the lung. Bile duct epithelial cells are known to play important roles in liver regeneration and immune response [54]. These results suggested that the liver injury occurred in COVID-19 patients may be due to the damage to bile duct cells, but not liver cells by the virus infection. Besides, the inflammatory cytokine storm was observed in severe COVID-19 cases [55], yet whether it results in liver damage in patients remains to be investigated. Postmortem biopsies were recently performed in a death COVID-19 patient, and the results

showed moderate microvascular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury [56]. Similar to the situation in SARS, antibiotics, antivirals and steroids are widely used for the treatment of COVID-19 [57]. These drugs are all potential causes of liver injury during COVID-19, but not yet being evident [49]. Actually, a recent study reported that the liver injury observed in COVID-19 patients might be caused by lopinavir/litonavir, which is used as antivirals for the treatment of SARS-CoV-2 infection [43]. So far, there is a lack of reports that liver failure occurs in COVID-19 patients with chronic liver diseases, such as chronic hepatitis B or C.

## Conclusion

In this review, we summarized the reports of liver injury caused by SARS-CoV, MERS-CoV, and SARS-CoV-2 infection (Table 2). The mechanisms of liver injury that occurred during SARS-CoV-2 infection remain largely unclear. Our current understanding suggests that infection of highly pathogenic human coronavirus may result in liver injury by direct virus-induced cytopathic effects and/or immunopathology induced by overshooting inflammatory responses. Meanwhile, SARS-CoV may aggravate liver injury in patients with viral hepatitis, but there is no evidence for MERS-CoV and SARs-CoV-2. Importantly, drug-induced liver injury during the treatment of coronavirus infection should not be ignored and needs to be carefully investigated. From a clinical perspective, in addition to actively dealing with the primary disease caused by coronavirus infection, attention should also be

paid to monitor the occurrence of liver injury, and to the application of drugs which may induce liver damage, such as antibiotics of macrolides or quinolone, and steroids, etc. Patients with liver damage are advised to be treated with drugs that could both protect liver functions and inhibit inflammatory responses, such as ammonium glycyrrhizinate[58], which may, in turn, accelerate the process of disease recovery.

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**Table1. Characteristics of SARS-CoV, MERS-CoV and SARS-CoV-2**

| Virus | Disease | Genome sequence homology to SARS-CoV-2 | Receptor | Possible intermediate hosts | Route of Transmission | Human susceptibility | Mortality (%) |
|---|---|---|---|---|---|---|---|
| SARS-CoV | SARS | 82%[4] | ACE2[22] | Palm civets[59] | Droplets, contact[60] | People are generally susceptible[60] | 9.6%[60] |
| MERS-CoV | MERS | 50%[4] | DPP4[35] | Camel[3] | contact[61] | People are generally susceptible[61] | 34.4%[61] |
| SARS-CoV-2 | COVID-19 | - | ACE2[52] | Pangolin[62] | Droplets, contact[39] | People are generally susceptible[39] | *3.7%[39] |

Abbreviations: SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS, severe acute respiratory syndrome; ACE2, angiotensin converting enzyme II; MERS-CoV, the Middle East respiratory syndrome coronavirus; MERS, the Middle East respiratory syndrome; DPP-4, dipeptidyl peptidase -4; COVID-19, 2019 novel coronavirus disease; *Available from the website of WHO on March,6,2020.

**Table2. Characteristics of liver injury during SARS, MERS and COVID-19**

| Disease | Reference | Numbers of analyzed cases | Proportions of pre-existing liver diseases | Manifestations | Note |
|---|---|---|---|---|---|
| SARS | Chang et al.[6] | 346 | 2 (0.57%) | Mild to moderate elevation of ALT and AST | Non-survivors had a significantly higher level of AST than survivors. |
| | Liu et al.[7] | 259 | - | Abnormal ALT 146 (56.3%)<br>Abnormal AST 96 (37.1%) | - |
| | Lu et al. [8] | 250 | NA | Abnormal ALT 87%<br>Abnormal AST <50% | - |
| | Tie et al. [9] | 222 | - | 136 (61.7%) | The incidence of live injury in severe patients (74.4%) was markedly higher than that in mild patients (43.0%). |
| | Zhao et al. [10] | 169 | - | Abnormal ALT 62.5% | Liver injury mainly appeared in the second and the third week after disease onset |
| | Yang et al.[11] | 168 | 12 (7.1%) | Abnormal ALT 52.5%<br>Markedly decreased ALB | - |
| | Duan et al. [12] | 154 | 4 (2.6%) | 58 (37.7%) | The incidence of live injury in severe patients (48.4%) was markedly higher than that in mild patients (13.0%). |
| | Huang et al. [13] | 108 | 62 (57.4%) | 38/38(100%)，in patients with HBV infection<br>33/46 (71.7%), in patients without | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | pre-existing liver disease | |
| | Wang et al. [14] | 76 | 6 | Abnormal ALT 59 (77.6%)<br>Abnormal AST 66 (86.9%) | - |
| | Jiang et al. [15] | 60 | NA | Abnormal ALT 46 (76.6%)<br>Abnormal AST 24 (40.0%)<br>Abnormal TB 18 (30.0%)<br>Abnormal ALB 27 (45%) | Liver injury mainly appeared in the second week after disease onset |
| | Wu et al. [16] | 52 | 9(17.3%) | Abnormal ALT and AST 53% | Liver injury mainly appeared in the second week after disease onset |
| | Duan et al. [17] | 43 | 3（6.9%） | Abnormal ALT 33 (76.74%)<br>Abnormal AST 21 (48.83%) | Liver injury mainly appeared in the second and the third week after disease onset |
| MERS | Arabi Y M[30] | 330 | 21(6.4%) | Abnormal ALT 142/252 (56.3%)<br>Abnormal AST 197/227 (86.8%) | The incidence of live injury in non-survivors (91.3%) was significantly higher than that of survivors (77.9%) in ICU patients. |
| | Sad M et al. [27] | 70 | - | Liver dysfunction 22 (31.4%) | Low albumin was suggested as a predictor of disease severity. |
| | Assiri A M[32] | 47 | NA | Abnormal ALT 5 (11%)<br>Abnormal AST 7 (15%) | - |
| COVID-19 | Guan et al. [41] | 1099 | 23 (2.3%) | Abnormal AST, 168/757 (22.2%)<br>Abnormal ALT, 158/741 (21.3%)<br>Abnormal TB 76/722 (10.5%) | The proportion of abnormal AST in severe cases (39.4%) was markedly higher than mild cases (18.2%). |
| | Cai et al. [42] | 298 | 8 (2.7%) | 44 (14.8%) | The incidence of live injury in severe patients (36.2%) was markedly higher than |

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| | | | | that in mild patients (9.6%). |
| Fan et al. [43] | 148 | - | 75 (50.7%) | A higher proportion of patients with liver injury (56.1%) received lopinavir/ritonavir treatment than those without liver injury (25%). |
| Wang et al. [44] | 138 | 4 (2.9%) | Mild elevation of ALT and AST | - |
| Cao et al. [45] | 128 | - | Abnormal ALT and AST only in severe patients | - |
| Chen et al. [46] | 99 | NA | Abnormal ALT 28 (28%)<br>Abnormal AST 35 (35%)<br>Abnormal TB 18 (18%)<br>Abnormal ALB 97 (98%) | One patient showed severe liver injury (ALT 7590 U/L, AST 1445 U/L) |
| Shi et al. [47] | 81 | 7 (9%) | 43 (53%) | - |
| Xu et al. [48] | 62 | 7 (11%) | 10 (16.1%) | - |
| Yang et al. [49] | 52 | NA | 15 (29%) | No difference in the incidence of liver injury between survivors (30%) and non-survivals (28%). |
| Huang et al. [40] | 41 | 1(2%) | 15(31%) | The proportion of elevated AST levels of ICU patients (62%) was higher than non-ICU patients (25%). |
| Zhang et al. [50] | 82 | 2(2.4%) | 64(78%) | All patients were deceased cases. |
| Huang et al. [51] | 36 | NA | Abnormal ALT 4/30 (13.33%)<br>Abnormal AST 18/31 (58.06%)<br>Abnormal TB 4/31 (12.90%) | All patients were deceased cases. |

Abbreviations: SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; HBV, hepatitis B virus; ICU, intensive care unit; TB, total bilirubin