


REVIEW



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Liver injury during highly pathogenic human coronavirus infections

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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.

KEYWORDS

COVID-19, liver injury, MERS, SARS, SARS-CoV-2

1 | 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

Abbreviations: ACE2, angiotensin-converting enzyme II; AKP, alkaline phosphatase; ALB, albumin; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; COVID-19, 2019 novel coronavirus disease; CoVs, coronavirus; DPP-4, dipeptidyl peptidase-4; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCoV-229E, human coronavirus 229E; HCoV-HKU1, human coronavirus HKU1; HCoV-NL63, human coronavirus NL63; HCoV-OC43, human coronavirus OC43; HCV, hepatitis C virus; hDPP-4, human dipeptidyl peptidase-4; IFN- γ , interferon γ ; IL-1, interleukin-1; IL-10, interleukin-10; IL15, interleukin-15; IL17, interleukin-17; IL-6, interleukin-6; MERS, the Middle East respiratory syndrome; MERS-CoV, the Middle East respiratory syndrome coronavirus; MOF, multiple organ failure; RT-PCR, reverse transcription-polymerase chain reaction; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; TB, total bilirubin; TNF- α , tumour necrosis factor α ; WHO, the World Health Organization.

Ling Xu and Jia Liu contributed equally to this work.

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.

2 | 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 severe 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.^{19,20,21} 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

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 discussed.

Abnormal serum levels of cytokines and chemokines were found at the early stage of SARS-CoV infection in patients. Duan et al¹² 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}

3 | 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 low level of albumin was a predictor of disease severity.²⁷ Similar to the

TABLE 1 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% ^{a,39}

Abbreviations: ACE2, angiotensin-converting enzyme II; COVID-19, 2019 novel coronavirus disease; DPP-4, dipeptidyl peptidase -4; MERS, the Middle East respiratory syndrome; MERS-CoV, the Middle East respiratory syndrome coronavirus; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2.

^aAvailable from the website of WHO on March 6, 2020.

TABLE 2 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%) Abnormal AST 96 (37.1%)	—
	Lu et al ⁸	250	NA	Abnormal ALT 87% 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% 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 33/46 (71.7%), in patients without pre-existing liver disease	
	Wang et al ¹⁴	76	6	Abnormal ALT 59 (77.6%) Abnormal AST 66 (86.9%)	—
	Jiang et al ¹⁵	60	NA	Abnormal ALT 46 (76.6%) Abnormal AST 24 (40.0%) Abnormal TB 18 (30.0%) 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%) Abnormal AST 21 (48.83%)	Liver injury mainly appeared in the second and the third week after disease onset
	MERS	Arabi ³⁰	330	21 (6.4%)	Abnormal ALT 142/252 (56.3%) Abnormal AST 197/227 (86.8%)
Sad et al ²⁷		70	—	Liver dysfunction 22 (31.4%)	Low albumin was suggested as a predictor of disease severity
Assiri ³²		47	NA	Abnormal ALT 5 (11%) Abnormal AST 7 (15%)	—
COVID-19	Guan et al ⁴¹	1099	23 (2.3%)	Abnormal AST, 168/757 (22.2%) Abnormal ALT, 158/741 (21.3%) 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 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	—

(Continues)

TABLE 2 (Continued)

Disease	Reference	Numbers of analyzed cases	Proportions of pre-existing liver diseases	Manifestations	Note
	Cao et al ⁴⁵	128	—	Abnormal ALT and AST only in severe patients	—
	Chen et al ⁴⁶	99	NA	Abnormal ALT 28 (28%) Abnormal AST 35 (35%) Abnormal TB 18 (18%) 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%) Abnormal AST 18/31 (58.06%) Abnormal TB 4/31 (12.90%)	All patients were deceased cases

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

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 al³⁷ 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 applying liver-damaging drugs during the course of treatment.

4 | 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 diarrhoea. In severe cases, respiratory distress and/or hypoxaemia occurred 1 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% to 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 al⁵³ 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.

5 | 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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CONFLICT OF INTEREST

The authors disclose no conflicts of interest.

AUTHOR CONTRIBUTIONS

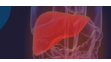
Xin Zheng designed and planned the work, and revised the manuscript. Ling Xu and Jia Liu performed the literature search and interpretation, and manuscript drafting. Mengji Lu and Dongliang Yang revised the manuscript.

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