ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2020 May 21; 26(19): 2276-2463



Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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World Journal of Gastroenterology

Volume 26 Number 19 May 21, 2020

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INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for *WJG* as 3.411 (5-year impact factor: 3.579), ranking *WJG* as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*

Proofing Production Department Director: *Xiang Li*

Responsible Editorial Office Director: *Ze-Mao Gong*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Subrata Ghosh, Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
May 21, 2020

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ONLINE SUBMISSION
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World Journal of Gastroenterology

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World J Gastroenterol 2020 May 21; 26(19): 2286-2293

DOI: 10.3748/wjg.v26.i19.2286

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Liver diseases in COVID-19: Etiology, treatment and prognosis

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Author contributions: Wu J and Song S wrote the manuscript, and contributed equally to this work; Cao HC contributed to the design, critically reviewed and revised the manuscript; Li LJ revised the draft; all authors reviewed and approved the final version.

Supported by Zhejiang University Special Scientific Research Fund for COVID-19 Prevention and Control, No. 2020XGZX052.

Conflict-of-interest statement: All the authors declare no competing interests.

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Manuscript source: Unsolicited manuscript

Received: April 22, 2020
Peer-review started: April 22, 2020
First decision: April 29, 2020
Revised: May 4, 2020
Accepted: May 14, 2020

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Abstract

In December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China causing coronavirus disease-2019 (COVID-19). Numerous studies have shown varying degrees of liver damage in patients infected with SARS-CoV-2. However, in previous case studies of COVID-19, the exact cause of liver injury has not been clearly elucidated, nor is there clear evidence of the interaction between liver injury and COVID-19. This study will analyze the causes of liver injury in COVID-19 and the influence of liver-related complications on the treatment and prognosis of COVID-19.

Key words: SARS-CoV-2; COVID-19; Liver injury; Etiology; Treatment; Prognosis

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Core tip: The study analyzed the causes of liver injury in coronavirus disease-2019, including direct effect of severe acute respiratory syndrome coronavirus 2 on the liver, drug-induced liver injury, and with underlying liver diseases, and talked about the therapeutic schedule, according to different etiologies. We believed it would be benefit to manage these patients well and improve their prognosis.

Citation: Wu J, Song S, Cao HC, Li LJ. Liver diseases in COVID-19: Etiology, treatment and prognosis. *World J Gastroenterol* 2020; 26(19): 2286-2293

Article in press: May 14, 2020
Published online: May 21, 2020

P-Reviewer: Paydas S, Perl A
S-Editor: Wang JL
L-Editor: A
E-Editor: Ma YJ



URL: https://www.wjgnet.com/1007-9327/full/v26/i19/2286.htm
DOI: https://dx.doi.org/10.3748/wjg.v26.i19.2286

INTRODUCTION

In December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China, known as coronavirus disease-2019 (COVID-19). Chan *et al*[1] found that the novel coronavirus genome sequence had an 82% homology with human SARS-CoV, and both SARS-CoV and SARS-CoV-2 infected cells *via* the angiotensin converting enzyme 2 (ACE2) receptor[2]. It is reported that up to 60% of SARS patients have abnormal liver function[3]. A recent epidemiological study showed that 43 cases of COVID-19 had varying degrees of liver function abnormalities, and higher alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level, and 1 of 99 patients with COVID-19 had serious liver damage[4]. The liver function abnormalities in COVID-19 patients were mainly manifested as abnormal levels of ALT or AST, with a slight increase in bilirubin levels. In a study of 69 patients by Wang *et al*[5], 23 had elevated ALT (33%) and 19 had elevated AST (28%). In the study by Cai *et al*[6], 44 of 298 patients (14.8%) had liver injury, and those with severe liver injury (36.2%) were more prone to these elevations than patients with mild liver injury (9.6%). According to the study by Zhang *et al*[7], the incidence of liver injury may be as high as 78% among 82 deaths of laboratory-confirmed SARS-CoV-2 infection. In this study, we analyzed the etiology of liver injury and the corresponding countermeasures to provide a reference for clinical management.

DIRECT EFFECT OF SARS-CoV-2 ON the LIVER

Liver damage in COVID-19 patients may be caused by the virus directly infecting liver cells. Previous studies have shown that some viruses that primarily target the upper respiratory tract also affect the liver, such as SARS-CoV, which causes SARS, and MERS-CoV, which causes Middle East respiratory syndrome[8]. In the study by Greenough *et al*[9], 90% of the patients infected with SARS-CoV had decreased lymphocytes, 25% had diarrhea, and 66% had elevated plasma liver enzyme concentration. Attention should be paid to the elevation in liver enzymes, and liver lesions in these patients. Liver cells expressing SARS-CoV protein were found in the deceased SARS patients. This indicated the possibility of direct viral infection of liver cells. In addition, autopsy results in patients with SARS showed a large number of mitotic liver cells, hepatocyte balloon degeneration, mild inflammation, moderate lymphocyte infiltration, steatosis, and central lobular necrosis, accompanied by obvious apoptosis[10]. By comparing cases of liver injury caused by SARS-CoV and MERS-CoV, Xu *et al*[11] pointed out that highly pathogenic human coronavirus infection can directly lead to liver injury, or it may be caused by an immunopathological reaction caused by excessive inflammatory response.

In the early stage of SARS-CoV-2 infection, approximately 2%-10% of COVID-19 patients had positive SARS-CoV-2 RNA in fecal and blood samples, accompanied by gastrointestinal symptoms such as diarrhea, abdominal pain, nausea and vomiting[12], which suggested that the virus may infect liver cells. Chau *et al*[3] demonstrated in their study that the liver biopsy of SARS patients showed a significant increase in mitotic cells, as well as eosinophils and balloon-like liver cells, which indicated that SARS-CoV may induce liver cell apoptosis and thus lead to liver damage. The study by Tan *et al*[13] showed that SARS-CoV-specific protein 7a can induce cell apoptosis in different organs (including lung, kidney and liver) through the caspase-dependent pathway, further confirming the possibility of SARS-CoV directly attack liver tissues and cause liver damage.

ACE2 is a receptor of the coronavirus on host cells that causes SARS. Several studies[14-16] have shown that SARS-CoV-2 can also bind to the ACE2 receptor, enabling the virus to replicate in cells. In addition, the expression level of ACE2 is very low in liver cells, accounting for 2.6% of the total number of cells, but highly specific in bile duct cells (59.7%), which is similar to the expression level in major targeted cells (type II alveolar cells) of SARS- CoV and SARS-CoV-2 in the lung[17,18]. Therefore, the novel coronavirus does not necessarily directly infect liver cells, but causes bile duct dysfunction by binding with bile duct cells, which play an important

role in liver regeneration and immune response. We therefore infer that liver injury may be induced by damage to bile duct cells caused by COVID-19.

In addition, cytokine storm caused by excessive immune response induced by the virus may also be one of the pathways of liver damage[19,20]. In most patients with severe COVID-19, there is an abnormal increase in serum proinflammatory cytokines. For example, Liu *et al*[21] observed an inflammatory cytokine storm in 40 confirmed COVID-19 patients, of whom 13 with severe COVID-19 had a significant and continuous decrease in lymphocyte count and an increase in neutrophil count. In particular, interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-17, and interferon-γ levels in critically ill patients continued to increase in peripheral blood[22,23]. Moreover, the T cell count and cytokine levels in patients with severe COVID-19 returned to the same level as those of patients with mild symptoms with gradual improvement in the disease[24,25]. Lu *et al*[26] proposed that lymphocytopenia and C-reactive protein levels were independently correlated with liver injury in COVID-19 patients, which showed that the main mechanism might involve an inflammatory cytokine storm. Cao *et al*[20] indicated that cytokine storms may cause shock and tissue damage in organs such as the heart, liver and kidney, and respiratory failure in severe cases. In addition, pathological changes such as spleen atrophy and lymph node necrosis were found, which suggested immune-mediated injury[27] (Table 1).

DRUG-INDUCED LIVER INJURY DURING TREATMENT OF COVID-19

Many studies[28,29] have shown that antibiotics (macrolides, quinolones), antiviral drugs (ribavirin), steroids and other drugs used to treat SARS patients may cause liver damage. In fact, antibiotics, antiviral drugs and steroids have been widely used to treat COVID-19, similarly to the SARS patients. Some of these drugs may potentially cause liver damage during the treatment of COVID-19[30]. A recent study[31] reported that the utilization rate of lopinavir/ritonavir in patients with newly developed liver injury was significantly higher than that in patients with normal liver function after admission. Importantly, abnormalities in liver function led to a longer hospital stay. Liver damage in COVID-19 patients may have been caused by the use of lopinavir/ritonavir as an antiviral treatment for SARS-CoV-2 infection. A multi-group clinical study[32] found that the degree of liver injury in COVID-19 patients was related to different clinical types, where mild and moderate patients had abnormally elevated ALT and AST, but the rate of elevation was much lower than that in severe and critically ill patients. Huang *et al*[33] showed that of 13 patients in the intensive care unit, 8 (62%) had increased AST, while of 28 patients who were not admitted to the intensive care unit, 7 (25%) had increased AST. The reason for this may be that severe and critically ill patients require long-term and more metered antiviral drugs, such as arbidol, lopinavir/ritonavir, *etc*. The results of this study showed that acute respiratory distress syndrome (ARDS) was an important factor for the death of COVID-19 patients, and early use of glucocorticoids reduced the risk of viral infection in patients with ARDS. The authors found that corticosteroid treatment did not influence virus clearance time, length of hospital stay, or duration of symptoms in patients with mild COVID-19. Zha *et al*[34] showed that 11 of 31 COVID-19 patients received corticosteroid therapy, and up to 70% of critically ill patients received systemic corticosteroid treatment, which indicated that corticosteroid use was associated with the severity of symptoms.

The guideline for diagnosis and treatment of SARS-CoV-2 issued by the National Health Commission of the People's Republic of China indicates that long-term treatment or use of a large amount of these drugs can cause adverse reactions in liver function, and liver damage due to the drug-induced hepatotoxicity.

COVID-19 COMPLICATED WITH UNDERLYING LIVER DISEASES

There are approximately 300 million patients with chronic viral hepatitis, cirrhosis, fatty liver, alcoholic liver disease or other liver diseases in China. Therefore, the influence of underlying liver diseases and the liver injury status in different COVID-19 patients should be carefully evaluated. Patients with chronic hepatitis B who have been treated with long-term nucleoside analogues are in the immune tolerance stage and have virus inhibition. When they are infected with SARS-CoV-2, they will have sustained liver damage. In patients with COVID-19 complicated with autoimmune

Table 1 Comorbidity with underlying liver diseases and liver dysfunction in coronavirus disease-2019 patients, *n* (%)

Ref.	Patients with SARS-CoV-2 infection	Patients with abnormal liver function	Patients with pre-existing liver co-morbidities	Abnormal indicators of liver function
Chen *et al*[4]	99	43 (43.4)	N/A	One patient with severe liver function damage: ALT 7590 U/L; AST 1445 U/L
Wang *et al*[5]	69	42 (60.9)	1 (1)	Abnormal ALT 33%; abnormal AST 28%
Cai *et al*[6]	298	44 (14.8)	8 (2.7)	Abnormal ALT 13.1%; abnormal AST 8.4%
Zhang *et al*[7]	82, deaths	64 (78.0)	2 (2.4)	Abnormal ALT 30.6%; abnormal AST 61.1%; abnormal total bilirubin 30.6%
Wang *et al*[14]	138	55 (39.9)	4 (29)	Abnormal ALT 17.4%; abnormal AST 22.5%
Lu *et al*[26]	85	33 (38.8)	6 (7)	-
Yang *et al*[30]	52	15 (28.9)	N/A	-
Fan *et al*[31]	148	75 (50.7)	6 (8)	Abnormal ALT 18.2%; abnormal AST 21.6%
Huang *et al*[33]	41	15 (36.6)	1 (2)	-

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

hepatitis, special attention should be paid to the effect of glucocorticoids on prognosis of the disease. Because of the high level of ACE2 receptor expression in bile duct cells, COVID-19 patients complicated with cholangitis may have aggravated cholestasis, resulting in increased levels of alkaline phosphatase and gamma glutamyl transpeptidase. Patients with liver cancer or cirrhosis of the liver are more likely to be infected with the virus as their immune function is relatively lower.

Previous studies[35] have shown that SARS patients with hepatitis B virus (HBV), hepatitis C virus infection were more likely to develop severe hepatitis, which may be due to increased viral replication during SARS-CoV infection. It was previously reported[36] that chronic hepatitis B patients with SARS-CoV infection may take longer to clear the virus from their bodies. Zha *et al*[34] found an association between chronic HBV infection and the time required for the clearance of SARS-CoV-2. The mechanism may be due to T cell dysfunction in patients with chronic HBV infection in response to other viruses, but the connection between them requires investigation. In a study of 1099 COVID-19 patients[37], 23 (2.1%) had HBV infection. Patients with severe illness were more likely to be infected with HBV than those without severe illness (2.4% *vs* 0.6%). Our unpublished study of 70 patients with COVID-19 combined with HBV infection showed the characteristics of a higher rate of liver injury, coagulation disorders, severe/critical tendency, increased susceptibility and increased viral replication during SARS-CoV-2 infection. Musa *et al*[38] have indicated that those at high risk of severe COVID-19 are generally older and/or associated with complications such as diabetes, cardiovascular disease and hypertension, which were similar to those at high risk of developing non-alcoholic fatty liver disease, making them more vulnerable to liver damage. Considering the expression of ACE2 receptor in bile duct cells, whether SARS-CoV-2 infection aggravates cholestasis in patients with primary biliary cholangitis requires further study. In addition, patients with cirrhosis and liver cancer with systemic immunodeficiency may be more vulnerable to SARS-CoV-2 infection[39]. Michaels *et al*[40] recently described the possible risks associated with transplantation in SARS-CoV-2 positive recipients, as liver transplantation may involve donor-to-recipient transmission of the virus.

TREATMENT OF LIVER DISEASES IN COVID-19 PATIENTS

According to the Chinese Pharmaceutical Association, COVID-19 patients with significant liver damage should be treated with hepatoprotective, anti-inflammatory, and jaundice-reducing agents such as polyene phosphatidyl choline, glycyrrhizic acid, bicyclol, and vitamin E. The treatment in critically ill patients should be chosen according to liver function injury and may include 1-2 kinds of drugs in order to avoid aggravating liver burden and interactions between drugs[34]. Recently, Chen *et*

al[41] reported that glycyrrhizic acid derivatives may also have antiviral activity against SARS-CoV-2. Glycyrrhizin was the preferred anti-inflammatory drug to protect against liver disease and has been used in clinical practice for many years.

The study by Zhang *et al*[42] showed that 2%-11% of COVID-19 patients had liver complications. However, the relationship between the presence of liver damage after COVID-19 infection in patients with preexisting liver disease requires further investigation. In COVID-19 patients with liver injury, the primary treatment is targeted to COVID-19, using antivirals, rational oxygen therapy, anti-infective agents, and symptomatic support. COVID-19 patients with mildly abnormal liver function generally do not need anti-inflammatory and hepatoprotective drugs. For patients with acute liver injury, the clinician should first analyze the probable cause of injury, and then take the corresponding measures. Hepatoprotective drugs should be administered prudently, and the types of drugs should be no more than two. In patients with COVID-19 who are suspected of having liver damage caused by antiviral drugs, discontinuing or reducing the dose of the drug should be considered. In addition, liver function indicators should be closely monitored to prevent the occurrence of acute liver failure. In patients with acute liver failure, intensive disease monitoring, and symptomatic and supportive treatment should be given, and active treatment for the etiology of liver failure should be administered.

PROGNOSIS OF PATIENTS WITH LIVER DISEASES IN COVID-19

Current studies[43,44] have shown that poor prognosis in COVID-19 patients was related to gender (male), age (60 years), underlying diseases (hypertension, diabetes, cardiovascular diseases), secondary ARDS and other related factors. An increase in neutrophil count and the neutrophil to lymphocyte ratio usually indicates a higher degree of disease severity and a poorer clinical prognosis. It was found that there were no independent correlations between ALT, AST, total bilirubin, alkaline phosphatase, albumin and other liver function indicators, and severe COVID-19[45], indicating that the liver was not the main target organ. However, ALT, AST, total bilirubin and other liver function indices were significantly increased in patients with severe COVID-19 compared to patients with mild COVID-19, and the liver function indices gradually returned to normal during recovery. Liver damage in patients with mild COVID-19 is often temporary and can be restored to normal without any special treatment[42]. Hepatoprotective drugs were usually given to those patients with severe liver damage. In addition, liver dysfunction in COVID-19 patients was associated with activation of the clotting and fibrinolytic pathways, a relatively low platelet count, an increased granulocyte count and neutrophil/lymphocyte ratio, and high ferritin levels. Although these parameters were considered nonspecific markers of inflammation, they also corresponded to a failure of innate immune regulation. It is worth noting that this change in immune balance occurred with age; thus, the situation may be worse for older patients[46]. The effect of glucocorticoid administration on the prognosis of COVID-19 patients with autoimmune hepatitis is unknown. For severe COVID-19 patients, more intensive monitoring or individualized treatment is required, especially in elderly patients with other complications.

CONCLUSION

Liver injury is common in COVID-19 patients, which may be caused by viral infection of bile duct cells or functional impairment caused by the use of antiviral drugs. However, the report by Xu *et al*[47] on a pathological study of COVID-19 patients showed moderate microvascular steatosis and mild inflammation in the hepatic lobular portal region, and no direct killing effect of the virus on the liver was found in the autopsy pathological results. In addition, inflammatory cytokine storms have been observed in severe COVID-19 cases, but whether they cause liver damage remains to be investigated. More attention should be focused on the liver function status of patients with COVID-19. In patients with liver diseases, on the one hand, attention should be paid to changes in the primary liver disease, and the monitoring and evaluation of liver function in patients with severe diseases should be intensified during treatment. On the other hand, we should carefully identify the causes of liver injury in combination with the pathophysiological changes caused by COVID-19. On the basis of active treatment of the primary disease, liver protection treatment should be administered to reduce liver injury.

ACKNOWLEDGEMENTS

We thank the authors of the primary studies for their timely and helpful responses to our information requests.

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